

ANNALS OF INTERNAL MEDICINE

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PUBLISHED MONTHLY BY

The American College of Physicians

Publication Office: Prince and Lemon Sts., Lancaster, Pa.

Executive Office: 4200 Pine Street, Philadelphia, Pa.

VOL. 25 (O.S., Vol. XXIX)

DECEMBER, 1946

NUMBER 6

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Subscription per volume or per annum, net postpaid, \$7.00, United States, Canada, Mexico, Cuba,
Canal Zone, Hawaii, Puerto Rico; \$8.00, other countries.

Entered as Second Class Matter August 21, 1933, at the Post Office at Lancaster, Pa., under the
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ANNALS OF INTERNAL MEDICINE

VOLUME 25

DECEMBER, 1946

NUMBER 6

EOSINOPHILIA IN MALIGNANT TUMORS: ITS SIGNIFICANCE *

By NORMAN H. ISAACSON, M.D., and PAUL RAPOPORT, M.D.,
Brooklyn, New York

EHRlich,²⁰ in 1860, was the first to stain and definitely describe the eosinophile, though previous investigators^{29, 30} seem to have recognized the coarse granules in the unstained cells. Ehrlich believed that eosinophiles originated and matured in the bone marrow and were delivered into the circulating blood as a definite cell type. This concept is still considered to be correct.

Most hematologists^{21, 22, 23, 26} today agree that 6 per cent of the total white cell count is the upper limit of normal for eosinophilic leukocytes. Kirk²⁴ recently made an extensive review of the literature on eosinophilia and reported an eosinophile count of over 6 per cent in the following conditions: (1) Allergic diseases of all types. (2) Certain skin diseases, such as mycosis fungoides, dermatitis herpetiformis, pemphigus, etc. (3) Parasitic infestations. Eosinophilia occurs in Hodgkin's disease, leukemia, periarteritis nodosa, benzol poisoning, Simmonds' disease, scarlet fever and Loeffler's syndrome. It has been observed in patients on a raw liver diet and in others after splenectomy.

Another cause of eosinophilia, which is either omitted or scarcely mentioned in modern hematology texts or treatises on the subject, is malignancy. Rheinbach¹ in 1893 was the first to report such a case. His patient had a malignant tumor of the neck and cervical lymph nodes with a white blood cell count of 120,000 cells per cu. mm., 40 per cent of which were eosinophiles. No histological sections of the tumor were taken, but the disease clinically was not leukemia. Since then there have been 18 case reports of eosinophilia with malignancy.† Most of these reports appear in the foreign literature

* Received for publication March 16, 1946.

From the departments of Laboratories and Medicine, Jewish Hospital of Brooklyn, Brooklyn, N. Y.

† Collins and Kaplan's²⁷ case was omitted since no operation or autopsy report was available to confirm their diagnosis.

and only a few in the American journals. These are listed chronologically in the chart below (table 1).

Many theories as to the cause of eosinophilia in malignant tumors have been advocated. Early investigators^{2,5} attributed it to necrosis of tumor tissue, the products of protein breakdown causing an eosinophylotactic re-

TABLE I
Previous Cases of Eosinophilia in Malignant Tumors

Author	Date	White Count	Eosinophiles	Type of Tumor	Metastases
1. Rheinbach	1893	120,000	40%	Primary site unknown	Cervical lymph nodes
2. Kappis	1907	43-50,000	33-39%	Bronchogenic carcinoma	Regional lymph nodes, ribs and sternum
3. Dunger	1910	35,000	65%	Carcinoma of colon	Lymph nodes, omentum
4. Strisower	1913	15,000	45%	Carcinoma of uterine fundus	Liver, lymph nodes, pleura
5. Czaki	1921	31,200	30%	Carcinoma of colon	Liver, lymph nodes
6. Schellong	1922	16,800	11%	Carcinoma of common bile duct	Liver, lymph nodes
7. Weiss	1926	6-16,000	4-31%	Adenocarcinoma of stomach	No metastases, but not ruled out
8. Netchaeff*	1929			Carcinoma of thyroid gland	
9. Pisa	1931	72,000	45%	Sarcoma surrounding the pancreas	Lymph nodes, liver, spleen
10. Roca de Viñals*	1931			Epithelioma of penis	
11. Chiray and Baudouin	1931	7-26,000	19-70%	Carcinoma of head of pancreas	Lymph nodes, liver
12. Sterling and Okumewski*	1932			Carcinoma of uterine cervix	
13. Paviot, Levrat and Guichard	1935	90,000	74%	Perirenal reticulosarcoma	Throughout abdomen
14. Riopelle	1936	10-15,000	62%	Pancreatic carcinoma (?)	Liver, lymph nodes, lungs
15. Sala and Stein	1937	18-36,000	52-70%	Carcinoma of uterine cervix	Adnexa, lymph nodes
16. Basnuevo, Suttar and Portella*	1937			Carcinoma of penis	
17. Morgan and Ballinger	1938	21-40,000	1-17%	Primary site unknown	Liver
18. LaManna and Borghetti	1938	9,000	10%	Fibrosarcoma of face	Skin, muscle, kidney
19. Scheer	1939	not stated	6-53%	Scirrhus gastric carcinoma	Throughout abdomen

* Cases quoted by other authors in foreign journals. Original articles not available in American libraries.

sponse. Others attributed it to bone marrow metastases with consequent stimulation of eosinophile production at that site, although osseous involvement could not be demonstrated in all cases. Strisower⁴ made the startling assertion that the eosinophilia was due to a vagal reflex. His patient had a hepatoma which metastasized to the cervical lymph nodes and compressed

the vagus nerve. The eosinophilia disappeared after removal of the nodes. However, after a brief remission, the eosinophile count again returned to its former level. Paviot¹³ and his co-workers suggested an origin from the connective tissue surrounding the tumor, since local tissue eosinophilia in malignant tumors has been reported many times. They further justify this statement by the finding of mononuclear eosinophilic cells in the blood stream in their case. Pisa⁹ claimed a familial eosinophilic predisposition is necessary to provoke an eosinophilic response to malignant tumors, the foreign protein of the tumor cells being the provocative agent. Weiss,⁷ however, experimentally injected extracts of tumor tissue and of blood from a patient who showed a hypereosinophilia into guinea pigs, rabbits and dogs. In no case was an increase in eosinophiles observed.

In the following pages we wish to report 15 cases of eosinophilia found in a review of 2363 cases of malignancy at the Jewish Hospital of Brooklyn in the last eight years. Included are cases of carcinoma of the breast and adrenal in which eosinophilia has hitherto not been reported.

CASE REPORTS

I. *Bronchogenic Carcinoma: Case 1.* C. L., a 70 year old white male, was admitted to this hospital on October 26, 1945 with colicky epigastric pain of three weeks' duration and jaundice for one week. On admission he was jaundiced, acutely ill and disoriented. He presented bilateral painless anterior and posterior cervical lymphadenopathy. The lungs were clear, the abdomen distended, with shifting dullness, and a fluid wave present. There were ecchymoses over the chest and extremities and bleeding gums. The stools were tarry.

A blood count done at home showed 80,000 white blood cells of which 18 per cent were eosinophiles. On admission to the hospital he had a hemoglobin of 84 per cent, red blood cells 4.6 million per cu. mm., white blood cells 120,000 per cu. mm. with 44 polymorphonuclears, 26 band forms, 3 myelocytes, 2 lymphocytes, 1 monocyte and 24 eosinophiles. The platelets were diminished. The following day his white blood cell count had increased to 140,000 per cu. mm. with 32 per cent eosinophiles. Stool examinations were reported as negative for ova and parasites on three occasions. A tentative diagnosis of eosinophilic leukemia was made, but before bone marrow studies could be done the patient died.

At autopsy, the patient had a carcinoma of the eparterial branch of the right upper lobe bronchus with metastases in the cervical, supraclavicular, axillary, inguinal, tracheobronchial, posterior mediastinal, retroperitoneal and mesenteric lymph nodes. There were metastatic nodules in the liver, kidneys and thyroid gland. There were diffuse metastases to the vertebral column and microscopic metastases in the spleen. Necrosis was present in all the tumor nodules, but tissue eosinophilia in the region of the tumor was not demonstrable.

II. *Carcinoma of the Gall-Bladder: Case 2.* G. B., a 55 year old white female, entered this hospital on July 5, 1938, complaining of pain in the right lumbar region of four months' duration. The positive physical findings were a moderate hypertension and a firm tubular mass palpable in the right upper quadrant. Oral and intravenous cholecystography was performed but failed to visualize the gall-bladder. Jaundice first appeared on July 31 and an exploratory operation was carried out four days later. At operation an indurated mass was found in the fundus of the gall-bladder and a firm umbilicated nodule in the right lobe of the liver. A cholecystostomy was per-

formed. The patient grew progressively worse post-operatively. On August 25 she vomited 1500 c.c. of blood, went into shock, and died. Autopsy revealed carcinoma of the gall-bladder with metastases in the lymph nodes, and liver and gastric ulcer with hemorrhage. No metastases to bone were demonstrable. The tumor showed slight necrosis but no eosinophilic infiltration. Her blood counts in the hospital averaged 6,000 leukocytes per cu. mm. with 11 per cent eosinophiles.

III. *Carcinoma of the Head of the Pancreas: Case 3.* F. H., a 57 year old colored male, was admitted to this hospital on August 9, 1939 with a history of clay colored stools for one month, icterus of skin and mucous membranes and dark brown urine for three weeks and a 20 pound weight loss during the two weeks prior to admission. Physical examination confirmed the presence of jaundice, and a nodular liver was palpated four fingers' breadth below the xiphoid process. At exploratory laparotomy on August 22, a firm irregular mass was found in the head of the pancreas with several metastatic nodules distributed throughout the liver. A cholecysto-duodenostomy was performed. The post-operative course was uneventful, and the patient was discharged on September 10, 1939. There was no follow-up. His white blood cell counts in the hospital averaged 11,000 per cu. mm. with 11 per cent eosinophiles.

Case 4. G. L., a 59 year old white female, was first admitted to this hospital in June 1938 because of sudden onset of headache and vomiting. She had slight nuchal rigidity and increased reflexes in the lower extremities. A spinal tap was performed and the spinal fluid contained many red blood cells. A diagnosis of subarachnoid hemorrhage was made. At this time she had a white blood cell count of 5300 per cu. mm. with 8 per cent eosinophiles. After three weeks of hospitalization she was discharged improved.

She was readmitted in September 1938 because of recurrence of headache. No abnormal neurological findings were present at this time. A white blood cell count showed 6200 per cu. mm. with 10 per cent eosinophiles. She left the hospital after one week without a further diagnosis being made. One week later, while at home, she began to complain of abdominal cramps. A gastrointestinal series done at this time showed an increased duodenal sweep indicative of enlargement of the head of the pancreas. Shortly thereafter her liver became enlarged and nodular, and ascites developed. Roentgenograms of the lungs and spine showed multiple metastatic nodules in both. Finally in February 1939 she developed numbness and weakness of the right side of the body and lapsed into coma. Her blood count on this last admission showed 5700 leukocytes per cu. mm. with 12 per cent eosinophiles. She died February 27, 1939. No autopsy was obtained.

IV. *Carcinoma of the Colon: Case 5.* A. W., a 41 year old white male, was admitted on August 9, 1945 complaining of right upper quadrant pain of seven weeks' duration. A tender liver was palpable just below the costal margin. Barium enema and a gastrointestinal series were negative, as was a digital rectal examination. His liver increased in size and became nodular. Increasing jaundice developed. At exploratory laparotomy on August 24, a firm fixed mass was palpable high in the rectum with metastatic nodules in the liver, omentum and regional lymph nodes. Biopsy of a liver nodule confirmed the diagnosis of carcinoma. His white blood cell counts in the hospital averaged 19,000 per cu. mm. with 12 per cent eosinophiles.

Case 6. N. K., a 62 year old white female, was admitted to this hospital on June 11, 1940 complaining of obstipation, abdominal distention and pain in the abdomen and back for nine days. Barium enema revealed an annular constricting lesion of the sigmoid colon. After decompression with a Miller-Abbott tube a first stage Mickulicz operation was performed. A constricting adenocarcinoma of the sigmoid colon was found with metastases in all the mesenteric lymph nodes. Histologic examination of the tumor showed necrosis but no eosinophilic infiltration. Her white blood cell counts in the hospital averaged 11,000 with 14 per cent eosinophiles. After 56 days in the hospital she was discharged. There was no follow-up.

Case 7. P. C., a 34 year old white female, entered the hospital on March 26, 1944 complaining of a lump in the right breast of one year's duration and epigastric pain for four months. She had had two previous admissions to this hospital, and her blood counts then showed no eosinophilia. On this admission she had a palpable mass in the right lower quadrant, and a barium enema revealed a napkin ring defect of the hepatic flexure. At operation this was found to be a carcinoma of the hepatic flexure with metastases in the regional lymph nodes. Necrosis and eosinophilic infiltration were both present in the tumor. A resection and primary anastomosis were performed. The lump in the breast was removed and this proved to be a fibroadenoma. Her blood counts on this admission averaged 8000 leukocytes per cu. mm. with 14 per cent eosinophiles. She was discharged. There was no follow-up.

Case 8. H. W., a 40 year old white female, entered the hospital on May 23, 1941 complaining of abdominal cramps, alternating diarrhea and constipation and bleeding per rectum, all for six weeks, with a weight loss of 10 pounds in the past four weeks. A mass was palpable rectally. On May 26, a perineal resection was performed, and microscopic examination of the mass removed confirmed the diagnosis of carcinoma. No necrosis or tissue eosinophilia was present. No evidence of metastases could be found in the limited operative field. Her white blood cell counts averaged 9000 per cu. mm. with 10 per cent eosinophilia. There was also a basophilia of 2 to 6 per cent. Two previous hospital admissions for other complaints showed no eosinophilia higher than 2 per cent. The patient was discharged 14 days post-operatively. There was no follow-up.

Case 9. A. S., a 67 year old white male, was admitted on October 30, 1941 with rectal bleeding of four months' duration. Sigmoidoscopy revealed a firm ulcerated mass in the rectosigmoid, and a barium enema showed a filling defect in this area. On November 9 a Rankin obstructive resection was performed. Metastases had occurred to the pre-aortic lymph nodes but not elsewhere in the abdomen. Microscopic examination of the tumor showed an adenocarcinoma infiltrated with eosinophilic cells. The white blood cell counts averaged 9000 per cu. mm. with 10 per cent eosinophiles.

On April 7, 1942 the patient returned for closure of the colostomy. He was otherwise well. His white blood cell count at this time was 8600 with 1 per cent eosinophiles. There was no further follow-up.

V. Carcinoma of the Stomach: Case 10. R. G., a 42 year old white female, was admitted to this hospital in October 1938 with pallor and weakness but no gastrointestinal complaints. She had a hemoglobin of 27 per cent, a red blood count of 2.78 million per cu. mm., a white blood cell count of 9000 per cu. mm. with no eosinophiles. Gastric analysis revealed no free hydrochloric acid. A gastrointestinal series showed an annular carcinoma in the pyloric region of the stomach. No metastases were noted at operation, at which time a subtotal gastrectomy and gastroenterostomy were performed. Histologic examination of the tumor showed necrosis but no eosinophilia.

The patient was readmitted in September 1939, with jaundice and right upper quadrant pain. The liver was enlarged to three fingers' breadth below the costal margin and was nodular. This time her blood counts showed a normal hemoglobin but a white blood cell count of 15,000 per cu. mm. with 13 per cent eosinophiles. Repeated examinations of the stools for ova and parasites were negative. She refused reexploration and left the hospital against advice on September 29, 1939. There was no follow-up.

VI. Carcinoma of the Breast: Case 11. M. M., a 30 year old white female, was admitted on April 10, 1943 complaining of a painless lump in her left breast with puckering of the overlying skin. A diagnosis of malignancy was confirmed microscopically after a radical mastectomy was performed. No necrosis or eosinophilia

was present in the tumor. Roentgenograms of the chest and long bones showed no demonstrable metastases, and the regional lymph nodes were not involved at operation. The blood counts at this time averaged 8000 leukocytes per cu. mm. with no eosinophiles. Post-operatively she received radiation therapy to her pelvis and an artificial menopause was induced.

She reentered the hospital on October 6, 1943 complaining of bouts of epigastric pain. Her white blood cell counts this time averaged 7500 per cu. mm. with 17 per cent eosinophiles. A gastrointestinal series, barium enema, gastroscopy and bone marrow studies were negative. The stool specimens showed no ova or parasites on repeated occasions. Trichina and echinococcus skin tests were negative. There was no history of allergy. Retrograde metastases to the abdominal lymph nodes were suspected but could not be proved. The patient was discharged without a further diagnosis having been established. There was no follow-up.

Case 12. J. S., a 54 year old white female, entered the hospital in January 1944 with a firm mass in her right breast which had been present for two months. A radical mastectomy was performed and the diagnosis of carcinoma was confirmed on histologic examination. No necrosis or eosinophilia was present in the tumor. The regional lymph nodes were free of metastases. Post-operatively she repeatedly complained of back pain, but roentgen examination of the spine, chest and long bones showed no abnormalities. One count taken in the hospital showed 7900 leukocytes per cu. mm. with 12 per cent eosinophiles.

She was given post-operative roentgen therapy in the out-patient department, and her white blood cell counts there averaged 6000 per cu. mm. with an eosinophilia of 12 to 14 per cent. In April 1944, a roentgenogram of the spine showed metastatic deposits in the lumbar region. She did not return to the clinic and could not be traced.

VII. Adenocarcinoma of the Adrenal Gland: Case 13. B. G., a 50 year old white female, entered the hospital in May 1942 with a prolapsed uterus, cystocele and rectocele. An incidental finding at this time was a palpable mass in the right flank. Intravenous and retrograde pyelography showed distortion of the upper calyces of the right kidney. The abdomen was explored, and a large retroperitoneal mass extending from the dome of the diaphragm to the iliac crest was found. This was removed together with the kidney. The microscopic examination was reported as adenocarcinoma of the adrenal gland without involvement of the kidney. There was extensive necrosis of tumor tissue but no marked infiltration with eosinophilic cells. No intra-abdominal metastases were found at operation. Roentgenograms of the lungs and spine showed no evidence of metastases. Her blood counts averaged 8500 leukocytes per cu. mm. with 12 per cent eosinophiles. The post-operative course was uneventful and she was discharged July 8, 1942.

She was followed in the out-patient department where she repeatedly complained of pain in her incision and generalized aches and pains. Her blood counts repeatedly showed 10 to 16 per cent eosinophilia. On March 6, 1945 a mass the size of a fetal head was found in the right mid-abdomen. Shortly afterward several masses were palpable along the aorta. The liver became enlarged and nodular. Roentgenograms of the chest revealed enlarged mediastinal nodes with metastatic nodules in the right lower and left upper lobes of the lung. The patient is still alive and receiving roentgen-ray therapy. She has lost a great deal of weight and is going rapidly downward. Her last blood count showed 8700 leukocytes per cu. mm. with 16 per cent eosinophiles.

VIII. Metastatic Carcinoma, Primary Site Undetermined: Case 14. J. S., a 69 year old white male, was admitted in January 1940 complaining of upper abdominal pain, constipation and a 20 pound weight loss in the eight weeks prior to admission. The stools showed occult blood on several occasions, but a barium enema and gastrointestinal series were negative. Physical examination showed only a

hypertension of moderate severity. His blood counts revealed an average of 12,000 leukocytes per cu. mm. with 15 per cent eosinophiles. At exploratory laparotomy the liver and omentum were studded with metastatic tumor nodules. Biopsy of the omentum revealed metastatic carcinoma. The patient left the hospital against advice seven days post-operatively and could not be further followed.

IX. *Lymphosarcoma: Case 15.* G. G., a 65 year old white female, entered the hospital on April 21, 1941 with painless swelling of the cervical and axillary lymph nodes of six weeks' duration. On physical examination she presented a moderate hypertension. The liver and spleen were just palpable beneath the costal margins. The peripheral blood showed a white cell count ranging from 9-15,000 per cu. mm. with an eosinophilia of 20 to 32 per cent. Bone marrow studies were normal as were stools for ova and parasites. Biopsy of a cervical node showed lymphosarcoma. The patient received radiotherapy post-operatively and was discharged improved, May 9, 1941. There was no follow-up.

All the above cases are summarized below (table 2).

TABLE II
Chart of Cases from Files of the Jewish Hospital of Brooklyn

Case No.	Type of Tumor	White Blood Cells/cu. mm.	Eosinophiles	Metastases
1	Bronchogenic carcinoma	80-140,000	18-32%	Liver, kidney, spleen, bone, lymph nodes
2	Carcinoma of gall-bladder	6,000	11%	Lymph nodes and liver
3	Carcinoma of pancreas	11,000	11%	Lymph nodes and liver
4	Carcinoma of pancreas	5,500	12%	Liver, lymph nodes, lung, brain, spine
5	Carcinoma of rectum	19,000	12%	Liver, omentum, lymph nodes
6	Carcinoma of colon	11,000	14%	Lymph nodes
7	Carcinoma of colon	8,000	14%	Lymph nodes
8	Carcinoma of rectum	9,000	10%	No metastases
9	Carcinoma of colon	9,000	10%	Lymph nodes
10	Carcinoma of the stomach	15,000	13%	Liver and lymph nodes
11	Carcinoma of the breast	7,500	17%	Lymph nodes?
12	Carcinoma of the breast	8,000	14%	Lumbar vertebrae
13	Adenocarcinoma of the adrenal	8,500	16%	Lymph nodes, lung, liver
14	Metastatic carcinoma, primary site unknown	12,000	15%	Liver and omentum
15	Lymphosarcoma	9-15,000	20-32%	Lymph nodes, spleen and liver involved

DISCUSSION

It should be emphasized that in each case repeated blood counts were made to confirm the presence of eosinophilia and that the eosinophilia was 10 per cent or more of the total white cell count. This was done so that accidental or coincidental eosinophilia could be excluded. With all extraneous causes eliminated, the incidence of eosinophilia in 2363 malignant tumors reviewed at the Jewish Hospital of Brooklyn during the last eight years was 0.54 per cent.

It is obvious that the occurrence of eosinophilia does not depend on the type of tumor involved. It occurs in malignant tumors of both epithelial

and connective tissue origin (29 epithelial, 5 connective tissue). Furthermore, the incidence of eosinophilia in each specific type of tumor corresponds closely to the relative frequency of occurrence of that type. There is no statistical difference in sex incidence, although it has been reported slightly more often in women (19 cases in women, 15 in men).

Thirteen of our 15 cases had metastases which were seen at operation or which became manifest shortly thereafter. A fourteenth case (Case 11) was suspected of having intra-abdominal metastases but this could not be proved. Similar findings were present in the cases previously reported in the literature. Fourteen of the 15 cases, in which details are available, had widespread metastases at the time of operation. The fifteenth case, that of Weiss,⁷ was a patient who had an adenocarcinoma of the stomach in which no metastases were found at the time of subtotal gastrectomy. The eosinophile count dropped to normal post-operatively but shortly returned to its elevated level.* Weiss stated that "Whether this post-operative eosinophilia was due to metastatic growth of the tumor could not be determined."

In two of our cases (12 and 13) pronounced eosinophilia was noted at the time of their first admission. In both these cases, no metastases could be demonstrated then, although they were carefully studied by roentgen-ray and other diagnostic means. The eosinophilia persisted and increased. At subsequent examinations widespread metastases became manifest.

One case, that of cancer of the stomach (number 10), showed an eosinophile count of zero at the time of gastrectomy and no metastases were found at this time. The patient was readmitted 10 months later with an eosinophilia of 13 per cent and metastatic nodules in the liver. Case 11 was similar. The patient had no eosinophilia at the time of radical mastectomy. Five months later, on readmission, she had an eosinophile count of 17 per cent and vague abdominal pains.¹ Intra-abdominal metastases were suspected but could not be proved. A thorough work-up failed to reveal the cause of her complaints. In both of the above cases, other causes of eosinophilia were ruled out.

Case 1 is interesting in that the metastases were so widespread, and the leukemoid reaction and eosinophilia so pronounced that a diagnosis of eosinophilic leukemia was made clinically.

From these facts certain conclusions can be drawn. In 27 of 30 cases of malignant disease with eosinophilia, metastases were present and in two it was suspected but not proved. In only a single case (number 8) was dissemination of the tumor neither suspected nor proved. There was no follow-up of the patient, however, and she might subsequently have developed demonstrable metastases as was the case in numbers 12 and 13. *Eosinophilia when it occurs with malignant tumors, and when other causes can be ruled out, is indicative of dissemination, and consequently significant of a poor prognosis.*

* This occurrence is not uncommon. It was first described by Vosswinkel²⁵ and later by Baradulin²⁶ and Strisower.⁴ Our case 9 illustrates this phenomenon.

Our study fails to throw further light on the pathogenesis of eosinophilia in malignant tumors. Of the 10 cases in which adequate study could be made of the primary tumor, six showed necrosis of tumor tissue (Cases 1, 2, 6, 7, 10 and 13), two showed local tissue eosinophilia (Cases 7 and 9) and three showed osseous metastases (Cases 1, 4 and 12). This would support any of the theories cited in the introduction to this article, but all have weaknesses, and no one explanation has yet been stated which would apply to all cases.

SUMMARY AND CONCLUSIONS

Nineteen cases of pronounced eosinophilia associated with malignant tumors are reviewed from the literature. To these are added 15 cases, making a total of 34. In 90 per cent of all the cases, metastases were present and in an additional 7 per cent they were suspected but not proved. In only one was metastasis neither demonstrable nor suspected. That dissemination may have been present though not clinically manifest is possible, as illustrated by two of our cases. Eosinophilia, when associated with a malignant tumor, with other causes ruled out, is indicative of dissemination of the malignant process.

The prevailing theories as to the pathogenesis of eosinophilia in malignant tumors are discussed. No definite cause has been established as yet.

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THERAPEUTIC TRIAL OF PENICILLIN IN TETANUS *

By LEON LEWIS, Comdr., MC, USNR, F.A.C.P., Berkeley, California

THE clinical usefulness of penicillin has been expanded through laboratory determinations of its antibacterial power in vitro and also through clinical trial in a great variety of infections in which there was frequently little reason to anticipate success. In the case of tetanus, studies in the laboratory have indicated that *Clostridium tetani* is affected by penicillin in fairly high dilutions. Abraham and his associates¹ report complete inhibition of *Clostridium tetani* grown in Lemco broth at a dilution of 1,000,000. This figure is the same as that given for *Staphylococcus aureus* by the same authors. Organisms grown in beef broth were inhibited at a dilution of only 100,000. Hobby, Meyer and Chafee² did not list *Cl. tetani* among the organisms susceptible to penicillin, but Herrell, Nichols and Heilman³ did. Robinson⁴ found growth of the organism completely inhibited in dilutions of 1:200,000 and partially in 1:400,000. However, there are no reports known to the writer of critical evaluation of the drug in human cases. Although it has been used in a few isolated instances, the patients have also reportedly received tetanus antitoxin and other adjuncts of therapy.⁵ It seemed important, therefore, to take advantage of an opportunity to study tetanus among the civilian casualties in the Okinawan campaign and to determine, if possible, whether penicillin had a place in the treatment of the disease. To this end Major (now Lt. Col.) Harvey G. Taylor arranged for a supply of penicillin from Army sources which was used in the following study.

Although the number of cases of tetanus treated in Military Government dispensaries and hospitals is not accurately recorded, it is estimated that over 300 were seen. When this investigation was undertaken early in July 1945, after the peak load of battle casualties had passed, 46 with tetanus were found in one of the large hospitals (G-6, 59) which had a patient load of over 1200 at that time. Unfortunately, the opportunity for clear-cut research was somewhat hampered by the type of cases then available. The most satisfactory case, assuming that the late symptoms of tetanus are due principally to fixed toxin, is the acute early one in which an antibacterial effect might be clearly recognized. Prompt arrest of development of symptoms followed by clinical improvement in such a patient would probably indicate susceptibility of *Cl. tetani* to penicillin in vivo. However, those with early acute tetanus generally failed to survive for transportation to the hospitals situated in the northern civilian areas or had already had the disease modified by treatment with antitoxin. From the group of patients available, those were selected

* Received for publication March 16, 1946.

TABLE I

Case Number	Age	Sex	Interval: Injury-Tetanus		Nature of Injury	Date of Injury	Date of Tetanus	Grade of Trismus	Local Tetanus	General Tetanus	History of Convulsions	Observed Convulsions
			Interval: Tet-Penicillin	Days								
1611	12	M	8	7	Mult. shrap.—head, l. arm	6-23	7-1	+++	—	+	—	—
962	27	F	17	4	Amp.—rt. mid-arm	6-17?	7-4	++++	—	++	—	—
1098	39	F	12	4	Shrap.—l. arm; burns—leg	6-22	7-4	++++	Rt. leg	+	—	—
1679	20	F	5	6	Rt. leg amp.—mult. shrap.	6-28	7-3	++++	Neck ++	++	—	++
1114	40	F	15	11	GSW—rt. knee	6-12	6-27	++++	Rt. lower ext.	++	—	—
728	49	F	14	6	Shrap.—ankle, buttocks	6-18	7-2?	+++	—	++	—	—
1265	22	F	12	4	GSW—l. thigh, rt. ankle	6-22	7-4	++	L. thigh	—	—	—
942	39	F	?	?	Scalp avulsion	6-22	?	++++	—	+++	—	—
2040	70	F	25	5	Shrap.—l. scapula, rt. leg	6-12	7-7	++++	—	++	—	—
990	21	F	20	10	Shrap.—lumbar, l. arm	6-8	6-28	+++	—	+++	—	—
*1998	17	M	4	4	GSW—l. buttock	7-1	7-5	+++	—	++++	+	++
1184	54	F	16	4	GSW—l. chest	6-18	7-4	++++	L. arm	+++	—	—
1431	27	F	42	3	Shrap.—rt. low ext.; partial amp.—rt. foot	5-23	7-5	+++	—	++	—	—
1526	47	M	22	6	Shrap.—l. eye and face	6-8	6-30	++++	—	+++	—	+
2093	22	F	?	?	Shrap.—l. thigh; GSW—leg	6-13	?	—	L. lower ext.	—	—	—

who had most recently developed symptoms and whose tetanus was not only severe but either untreated or unaffected by antitoxin. In most instances there were major infected wounds, and the difficulty of discriminating between death due to wounds and death due to tetanus was foreseen. However, the effect of penicillin in other diseases has often been dramatic, and the patients selected offered every opportunity for demonstrating a striking therapeutic effect.

The accompanying tables 1, 2, and 3 present in summary form the clinical data of 15 cases treated with penicillin, four treated with antitoxin of known amount, and 27 random cases, some of whose records failed to disclose the

TABLE II

1605	21	F	10	—	Shrap.—rt. thigh	6-18	6-28	++	—	—	—	—
1541	39	F	3	—	Amp.—rt. arm	6-17	6-20	+	—	+	—	—
881	20	F	10	—	Shrap.—rt. buttock	6-17	6-27	+	Rt. and l. lower ext.	+	—	—
*1997	19	M	10	—	GSW—rt. knee and l. thigh	6-24	7-4	++++	Rt. hamstring	++	—	+

* See case reports.

TABLE I.—Continued

Date	Tetanus Antitoxin Administered	Date	Tetanus Antitoxin Previously Administered	Date	Penicillin Administered	Result	Comment
—	None	—	None	7-8	460,000 U—120 hrs.	Recov.	Poor selection for trial
—	None	—	None	7-8	280,000 U—72 hrs.	Died 7-11	Febrile; necropsy neg.
—	None	—	None	7-8	500,000 U—116 hrs.	Recov.	Slow imp. after 7-16
7-15	80,000 U	—	None	7-8	500,000 U—116 hrs.	Died 7-24	Febrile; no necropsy
—	None	7-4 & 5	200,000 U	7-8	500,000 U—116 hrs.	Improved	Relaxed 7-15; free 7-26
—	None	6-30	20,000 U	7-8	500,000 U—116 hrs.	Recov.	Grad. imp. after 1st wk.
—	None	—	None	7-8	500,000 U—116 hrs.	Recov.	Grad. imp. after 1st wk.
7-15	6,000 U	6-25	40,000 U	7-8	500,000 U—116 hrs.	Died	No imp. 1st wk; mult. abscesses
—	None	—	None	7-11	710,000 U—87 hrs.	Recov.	Grad. imp.
—	None	—	None	7-8	500,000 U—116 hrs.	Recov.	Grad. imp. Infect. imp.
7-14	100,000 U I-V	—	None	7-9	650,000 U—124 hrs.	Recov.	No imp. with penicillin
—	None	—	None	7-8	500,000 U—116 hrs.	Died 8-1	Progressive tetanus
—	None	6-26	1500 U	7-8	500,000 U—116 hrs.	Improved	Grad. imp.
—	None	—	None	7-8	500,000 U—116 hrs.	Died 7-23	Persistent tetanus
7-15	20,000 U I-M	—	None	7-13	150,000 U—Locally	Improved	No reaction to trt.

exact dosage or date of administration of antitoxin. The latter group (table 3) was considered satisfactory to serve as a rough control. The penicillin-treated group and the four antitoxin-treated patients were kept under observation with the same general ward management. The others were not under direct supervision but were followed in other wards. Among the 15 patients who were given penicillin, there were three who had previously been injected with therapeutic amounts of antitoxin, and one had received a single prophylactic dose. These four were included in the group for clinical trial of penicillin since they had severe tetanus and had apparently failed to benefit from antitoxin.

TABLE II.—Continued

7-7	1,500 U I-M	?	113,500 U		Recov.	Progressive imp.
7-7	3,000 U I-M	?	?		Recov.	Progressive imp.
—	None	7-4	100,000 U		Recov.	Progressive imp.
7-9	100,000 U I-V	—	None		Recov.	Prompt response to trt.

TABLE III

Case Number	Age	Sex	Interval: Injury-Tetanus	Nature of Injury	Date of Injury	Date of Tetanus	Grade of Trismus	Local Tetanus	General Tetanus	History of Convulsions	Observed Convulsions
			Days								
2057	27	F	14	Comp. fract.—rt. femur	6-21	7-5	++	—	±	—	—
1561	54	F	30?	Shrap.—head, neck, chest	6-5?	7-4?	+++	—	+	—	—
1651	34	F	7	Shrap.—rt. foot, leg; l. shoulder	6-22	6-30	++++	—	+	—	—
1652	16	F	5	Shrap.—rt. knee, l. leg	6-17	6-22	+++	Rt. foot	++	—	—
1654	54	F	10	Shrap.—rt. forearm; temple	6-17	6-27	+++	—	+	—	—
1649	24	F	17	Shrap.—rt. thigh	6-12	6-30	+++	—	+	—	—
1653	20	F	13	Fractured—l. arm	6-11	6-24	+++	Slight	+	—	—
1647	36	F	17+	Shrap.—head	6-7+	6-24	++++	—	+	—	—
1739	16	M	21	Comp. fract.—l. leg	6-15	7-13	*++++	—	+	—	—
1627	66	M	10	Shrap.—l. leg, rt. arm	6-8	6-18	++++	Rt. forearm	+	—	—
1624	25	F	14	GSW—l. leg	6-8	6-22	++	—	—	—	—
1638	26	F	15	Shrap.—l. arm and leg	6-8	6-23	+++	—	++	—	—
1625	61	M	6	Shrap.—l. hand	6-18	6-24	+	—	+	—	—
1641	22	F	10	Shrap.—l. buttock; temple	6-18	6-28	+++	L. thigh	++	—	—
1640	41	F	10	Shrap.—rt. hand	6-18	6-28	+++	—	—	—	—
1170	18	M	4	Shrap.—rt. and l. feet	6-24	6-28	++++	Rt. low. ext.	+	+	+
1644	20	F	24	Shrap.—rt. shoulder	6-8	7-2	+++	—	+	—	—
1645	29	F	9	Amp. rt. arm	6-16	6-25	++++	—	+	—	—
1646	26	F	16	Shrap.—rt. hip	6-8	6-24	+	—	±	—	—
1639	39	F	15	Shrap.—rt. buttock	6-8	6-23	++	—	—	—	—
1636	28	F	15	Shrap.—rt. arm	6-13	6-28	++	—	+	—	—
795	17	M	7	Comp. fract.—l. leg	6-18	6-25	++	—	++	—	—
1635	24	F	10	Shrap.—both arms; rt. amp.	6-18	6-28	++	—	—	—	—
1667	30	F	12	Shrap.—back	6-18	6-30	+++	—	+	—	—
506	11	M	?	Comp. fract.—l. leg; shrap.	?	?	++++	Moribund	—	—	—
765	24	F	?	Shrap.—l. leg, rt. chest	?	?	+	—	++	—	—
1831	20	F	4	Comp. fract.—rt. arm; shrap.—rt. neck	6-28	7-2	++	—	Toxic	—	—

PENICILLIN TREATED GROUP

Three males and 12 females of ages varying from 12 to 54 years, all of them showing signs of severe tetanus, were selected for trial of penicillin. Nine were suffering from the effects of multiple or severe shrapnel wounds, four from gun-shot wounds, and one had the right arm amputated at the mid-humerus for an undetermined type of injury. All had open and infected

TABLE III.—Continued

Date	Tetanus Antitoxin Administered	Date	Tetanus Antitoxin Previously Administered	Result	Comment
?	1500 U on admission	—	None	Improved	Sl. trismus persists 7-13
7/4-7	33,000 U	—	None	Improved	Up and about 7-13
7-6 7-12	4,500 U 3,000 U daily, 4 days	?	2 inj. daily, 5 days	Recov.	Discharged well 7-23
7-12	3,000 U daily, 4 days	?	7 inj.; 1500 U on 7-6	Recov.	Up and about 7-26
7-12	3,000 U daily, 4 days	?	2 inj. daily, 3 days	Recov.	Discharged well 7-23
7-6	3,000 U I-V; 1500 U I-M	?	2 inj. daily, 5 days	Recov.	Condition good 7-13
7-6 7-12	3,000 U I-V; 1500 U I-M 3,000 U daily, 4 days	?	7 inj. in 5 days	Recov.	Up and about 7-26
7-12	3,000 U I-M	?	3 inj. in 2 days	Improved	Tetanus absent 7-26
7-14	80,000 U	—	None	Died 7-15	Died 3 days post-operative
—	None	?	2 inj. daily, 7 days	Recov.	Discharged well 7-15
—	None	?	8 injections	Recov.	Tetanus absent 7-26
—	None	7-3	1 inj. Dose?	Improved	Trismus and stiff neck persist 7-26
—	None	?	4 inj. in 4 days	Recov.	Tetanus signs absent 7-26
—	None	?	5 inj. Dose?	Improved	Moderate trismus persists
—	None	?	3 inj. in 2 days	Recov.	Discharged well 7-26
—	None	?	5 inj. in 5 days	Recov.	Tetanus signs minimal 7-26
—	None	?	1 I-V inj.	Improved	Tetanus subsiding 7-26
—	None	?	7 injections	Recov.	Discharged well 7-19
—	None	?	8 injections	Recov.	Minimal tetanus 7-26
6-28	1 inj. I-V, dose?	—	—	Recov.	Discharged well
—	None	?	2 inj. daily, 3 days	Recov.	Improved 7-13, well 7-26
—	None	?	1500 U prophylactic	Improved	—
—	None	?	7 injections	Recov.	Tetanus signs absent 7-26
—	None	?	5 injections	Recov.	Tetanus signs absent 7-26
—	None	—	No history	Died	Death from wound infection
6-22	1500 U	—	None	Died 7-11	Wounds chief cause of death
—	None	?	3 injections	Worse	Tetanus more marked 7-25

wounds, some of which were severe: avulsion of most of the anterior scalp (No. 942); loss of the left eye, most of the orbit and maxilla (No. 1526). One patient, a 12 year old male, proved to be a poor selection for this group since he began to improve rapidly before penicillin was started and would undoubtedly have recovered without treatment. Patient No. 2093 was the only one to receive only local injections of penicillin into the region of her wounds. In all other cases the intramuscular route was used.

Fourteen patients received 20,000 units of penicillin* intramuscularly every four hours (except during the interval 2200 to 0600, when only native nurses' aides were on duty in the wards), a total of 100,000 units in 24 hours, for approximately five days. In some instances larger doses were given more frequently toward the end of the course.

Seven patients recovered, five of whom had not received antitoxin at any time, one who received 20,000 units on June 30 and another (No. 1998) who was given 100,000 units intravenously on July 14 after having failed to improve under penicillin therapy. One patient, as noted above, had already improved considerably before penicillin was started (No. 1611). The other four who received no antitoxin but recovered (Nos. 1098, 1265, 2040, 990) showed gradual abatement of symptoms during the second week. There was no sharp alteration of clinical course during the period of treatment or within the first three or four days following injections of penicillin. In most instances the wounds became cleaner and in this respect treatment was undoubtedly beneficial and indicated. However, the course of tetanus seemed no different from that in the patients who had received only prophylactic antitoxin, and all the patients who recovered slowly seemed to have weathered the disease without much evidence of influence by treatment. The final patient of this group (No. 1998) who was given antitoxin after failure of penicillin will be discussed in detail in a comparison with a similar case treated immediately with antitoxin.

Five deaths occurred: Nos. 962, 1679, 942, 1184, 1526.

Case No. 962 was the only one examined post mortem. This patient had pronounced trismus, neck and back rigidity, and during the course of her illness developed dysphagia and later diarrhea. Her course was febrile and remained so although the amputation stump of the right humerus which exuded pus freely on July 8 was clean at the time of death. Necropsy showed no visceral lesion to account for the fever and was negative except for a small area of phlebitis of the deep pelvic veins and ascariasis. (Autopsy was performed by Lt. Comdr. Harold Fink, MC, USNR.) In the absence of other evident cause, this death may be attributed to tetanus, and it is significant that although tetanic symptoms were of only four days' duration there was no apparent abatement with penicillin therapy.

Patient No. 1679, a 20 year old female with multiple shrapnel wounds and amputation of the right leg, exhibited gradually more severe tetanus from onset to death. By the end of a week's observation it was obvious that penicillin had been ineffectual, and tetanus antitoxin in a dose of 80,000 units was administered intravenously. The clinical course was not significantly altered by this measure, resorted to on the twelfth day of tetanus, and the patient slowly deteriorated to die on the twenty-first day of the disease. In this instance the temperature ranged from 99.6° to 100.6° F. (rectal) until the twelfth day of tetanus at which time it rose to 104.4° F. and remained elevated for the remainder of the illness.

No. 942 was a debilitated 39 year old female whose scalp had been partially avulsed by a stone contusion. On July 8 the remaining parieto-occipital scalp was loose and free pus could be readily expressed. Following penicillin the infection cleared suf-

* The penicillin used was of the following manufactures and lot numbers: CSC-Commercial Solvents, Lot No. 44121801, Expiration date Dec. 1945. Squibb, Lot No. 3351-1, Expiration date Dec. 28, 1945. The sodium salt of penicillin was used throughout.

ficiently to permit surgical intervention. On July 13 Lt. Comdr. D. J. Kweder, MC, USNR, made multiple drill holes in the outer table of the skull with the object of permitting granulations to protrude from the diploe to make a base for subsequent skin grafting. Even while receiving penicillin, however, abscesses developed at the left elbow and later the left buttock. The latter lesion failed to heal after repeated incisions for drainage. There was no growth of granulations from the perforations of the skull. The patient gradually weakened. By July 26 she had less trismus than was present at the outset, and in the writer's opinion she would have recovered from tetanus had she not suffered the complicating infections. Death on August 9 was considered due principally to pyogenic infection. A culture from the pus of this lesion was reported to have shown "young forms (Gram positive rods) and suspicious tack-head types" of tetanus organisms on liquid thioglycollate medium.

Patient No. 1184, a 54 year old female, had a superficial wound of the left chest wall and showed extreme localized tetanus of the left arm and left side of the neck. The head was flexed and rotated sharply to the left, the upper back muscles were rigid, and motion of the chest was restricted. The patient was mentally alert throughout her illness and required sedatives and analgesics frequently. After a week tetanic spasm spread to involve the lower extremities, and later the abdomen became board-like and the trunk extremely rigid. The course of her illness was not influenced by penicillin. Death occurred on August 1, the twenty-seventh day of the disease.

When he was selected for therapeutic trial with penicillin patient No. 1526, a 48 year old male, seemed to have advanced tetanus and a destructive wound of the face. Later he developed pulmonary symptoms which complicated his illness and probably caused his death. As a result of shrapnel he lost the left eye, most of the orbit and part of the maxilla. The wound was an open granulating lesion with moderate secondary infection. Following penicillin treatment the granulations became cleaner and healthier appearing. However, trismus and stiffness of the back were followed by spasm of thoracic muscles and impairment of respiratory motion. Orthopnea developed on July 15 and persisted. The only finding on chest examination was impairment of resonance. Death occurred on July 23, on the twenty-fourth day of tetanus. Evaluation of the rôle of pulmonary disease as a cause of death would have been easier had necropsy been performed, but on the basis of the clinical findings there can be little doubt that tetanus was an important contributory cause.

Local injection of penicillin was given in one instance.

The administration of penicillin directly into the region of her wounds had no beneficial effect upon the localized tetanus in case No. 2093. Two injections, one of 60,000 units around a wound of the leg and 90,000 units into and around a wound of the thigh, were given on July 13. There was no improvement after 48 hours, and an injection of 20,000 units of antitoxin was given intramuscularly on July 15. Spasm of the leg muscles began to subside on July 19 and by July 26 only equinus contraction of the foot remained.

In summary, the 14 patients treated by intramuscular injection of approximately 100,000 units of penicillin daily for about five days failed to show any definite evidence of alteration of the clinical course of the disease which seemed attributable to therapy. Those who recovered exhibited no sharp amelioration of symptoms but slowly improved in the manner of other patients who received minimal doses of antitoxin. (See section on the rough control group of 27 patients.) Since the over-all mortality from tetanus among the civilian casualties is not known, no comparison can be

made on a statistical basis, but it was common knowledge that recovery not infrequently occurred without specific therapy.

COMPARISON OF PENICILLIN AND ANTITOXIN TREATMENT IN SIMILAR CASES

Perhaps the best opportunity for therapeutic evaluation occurred when, on July 9, two young male patients, Nos. 1997 and 1998, were admitted to the hospital. Both of these patients came down with acute tetanic symptoms within the preceding five days; both had wounds which were relatively simple and clean, and both exhibited about the same severity of symptoms: extreme trismus, generalized rigidity and convulsive seizures at frequent intervals—especially when subjected to sharp noises or physical shocks. The patient selected for treatment with penicillin most nearly satisfied the criteria considered desirable when the plans for this study were made: he had a simple and fairly clean wound; tetanus developed four days after injury and was acute and severe. The one chosen for antitoxin treatment had a longer incubation period (10 days as opposed to four) and the onset of tetanus was one day earlier. These cases are reported in detail.

Case No. 1998. An Okinawan farmer, age 17, male, was admitted from a Military Government dispensary on July 8 with a history of gunshot wound of the left buttock on July 1. Trismus developed on July 4 and rigidity of the muscles of the neck, back, abdomen and extremities became progressively worse from that time. Frequent extensor convulsive episodes associated with acute trismus occurred during observation and could be precipitated by touching the patient's cot or by making a loud noise. The only voluntary motions fairly easily accomplished were flexion and extension of the upper extremities. Otherwise the patient was in complete and continuous extensor rigidity. Attempted motion was extremely painful.

Penicillin was given intramuscularly in 20,000 unit doses every four hours (except at 0200; five doses in 24 hours) for 25 doses, then in 50,000 unit doses every three hours for an additional three injections. The total amount of penicillin administered was 650,000 units.

During the period of treatment it was necessary to resort to the use of barbiturates frequently. Even during the height of sedative action contractures could be readily precipitated. The patient's status showed very little alteration during the first week of observation and treatment. He did not become worse, although exhaustion became more pronounced, yet he showed no sign of remission. The degree of tetanus was remarkably constant, and there were no changes which could reasonably be ascribed to a therapeutic agent. Finally, on July 14, having concluded that penicillin had not been of benefit, a culture was made from the wound and later 100,000 units of tetanus antitoxin were given intravenously at 1830.

There was no change the following day, but within four days trismus subsided and muscular spasms ceased. On July 26 knee flexion of 15 to 20 degrees was first possible. The abdomen was less rigid and the neck was free. This was the last date of observation, but the patient was later reported to have made a complete recovery.

Unfortunately, facilities were not available for full identification of the organism cultured from the wound at the end of penicillin treatment, but an Army Station Hospital laboratory reported as follows on the culture taken July 14: "Few streptococci seen; occasional Gram-positive rod (young form of tetanus bacillus); no 'tack-head' forms seen."

Case No. 1997. An Okinawan male, age 19, admitted on July 8 with a history of bullet wounds of the upper left thigh and the right knee region. The injuries were sustained on June 24 and trismus was first manifested on July 4. By July 7 trismus was extreme, and generalized tetanic spasm had supervened. Acute spasms of the face and extremities occurred fairly frequently and could be precipitated by external stimuli. The degree of tetanus was not quite so severe but approached that shown by patient No. 1998.

At 1315 on July 8 the patient was given 100,000 units* of tetanus antitoxin intravenously. A brief period of rigor occurred at 1430, but there were no other reactions to the serum. Within four hours of the administration of antitoxin there was evident muscular relaxation. Local tetanus which had been pronounced in the right leg muscles diminished promptly, although it recurred on the third day. On the day following antitoxin injection there seemed to be some exacerbation of muscle tension, but following the second day there was progressive improvement, and convulsive phenomena did not occur after treatment was given. By July 26 the patient had almost fully recovered and was able to be up and about.

ANTITOXIN TREATED GROUP

The four patients selected for comparative observation with the penicillin treated group (see table 2) included case No. 1997 which is discussed above. Two others were selected because they had received large doses of antitoxin several days (nine and six respectively in cases No. 1605 and 881) after the onset of tetanus, and one (No. 1541) because she was apparently making a good recovery from severe tetanus following only 3000 units of antitoxin.

On July 8 there was fairly marked trismus and slight neck rigidity noted in patient No. 1605, a 21 year old female with shrapnel injury of the right thigh. She had been given 113,500 units of antitoxin at another hospital before admission and an additional 1500 units on July 7. There was noticeable improvement daily, and trismus as well as nuchal rigidity was no longer present on July 12. The shrapnel wound granulated well and healing progressed normally. Patient No. 1541, a 39 year old female, was admitted with the right arm amputated and with a history of tetanus of 17 days' duration. She had moderate neck rigidity and slight trismus, showed progressive improvement and was free of tetanus on July 15. The third patient, No. 881, a 20 year old female with a severe shrapnel wound of the right buttock, had moderate local tetanus of both lower extremities and slight neck rigidity and trismus. A large dose of antitoxin was given seven days after the onset of trismus, and improvement was progressive and satisfactory. On July 12 she was able to be up and about and by July 15 there was little evidence of tetanus.

OBSERVATION OF 27 CASES TREATED ON GENERAL SERVICE

Although this group of patients does not give a complete picture of tetanus among civilian casualties, it serves as a sort of background for the observations reported above. Tetanus of all degrees of severity occurred in patients with all manner of injuries and burns. The fulminating cases did not survive more than a few days, and none † of these was seen at the

* All antitoxin dosages given are in American units.

† Case No. 1739 may be an exception, but it was impossible to obtain reliable information because of his poor condition when first seen.

time of this study. Many of the milder cases recovered without antitoxin therapy. The dosage of antitoxin given the patients in this group depended upon many factors: the amount available at the hospital where treatment was first rendered, the number of patients under the care of each medical officer, and the organizational status of the hospital. At times only the most cursory type of medical attention could be given, especially in hospitals which were activated with scant notice or inactivated at the height of the emergency on various grounds of military necessity, or for other reasons.

As will be seen in table 3, all but one of the 27 patients are known to have had antitoxin. The dosages and dates of administration were frequently doubtful since most of the patients were transferred from other hospitals without records. Sixteen of these patients, most of whom had received inadequate antitoxin according to current standards, made complete recoveries, and seven others improved sufficiently to indicate probable ultimate recovery. Only three deaths occurred in this group, but one patient who became progressively worse while under observation probably terminated fatally. None of the three fatal cases came to necropsy.

Patient No. 1739, a 16 year old male with badly compounded fractures of the left tibia and fibula, was operated upon the day before he was first seen by the writer. He was found to be extremely ill and to have marked trismus and neck rigidity. Ward attendants were of the opinion that tetanus developed acutely following operation. Tetanus antitoxin in a single dose of 80,000 units was given on the second postoperative day, and the patient died the following day.

Patient No. 506, an 11 year old male with shrapnel wounds of the right shoulder and a compound fracture of the left leg, was moribund when first examined and no history was obtainable. There was no record of antitoxin therapy. The boy lay on his cot saying the word "maggots" over and over and many of the creatures of which he had learned the name were seen crawling out of the opening of the cast. Death occurred three days after the first examination, probably from wound infection and anemia. Tetanus was slight in degree.

The only other patient of this group who died, No. 765, a 24 year old female, had only slight evidence of tetanus and showed marked toxicity from her wounds: a shrapnel injury of the left leg and a large wound of the right chest. She was able to give little reliable information. Death occurred on the fifth day of observation and was considered the result of wounds and infection.

The last patient of this group, No. 1831, a 20 year old female with a compound fracture of the right arm and a wound of the right side of the neck, exhibited increasingly severe tetanus throughout the period of observation. There was marked stiffness of the neck and complete trismus, as well as pallor and evident toxicity. When last seen on July 26 a fatal outcome was anticipated.

DISCUSSION

The symptoms of tetanus are believed to be due to a diffusable exotoxin which reaches the motor neurons and neuromuscular end organs through the circulation.^{6, 7, 8} The circulating toxin exerts its effect upon spinal and medullary motor nerve cells and eventually some, it is thought, becomes irreversibly fixed to the cells. It is obvious, therefore, that a purely anti-

bacterial agent cannot be expected to produce immediate mitigation of clinical symptoms. Antitoxin, which has a direct effect upon the symptom-producing agent, would be expected and actually does frequently produce such amelioration, although its effect may be minimal in late cases. Recovery from the bacterial infection cannot, however, be reasonably ascribed to antitoxin and must be due to natural mechanisms for overcoming the *Clostridium*. Conceivably, therefore, an effective antibacterial agent could influence both the clinical course and the rate of recovery from tetanus by inhibiting the growth and toxin production of the organisms. The manifestations of those influenced would, of course, be most marked in an early infection but, conceivably, mortality reduction might be manifested in a large group of patients with tetanus of varied duration.

The difficulty of selection of early, uncomplicated cases of tetanus at the time of this investigation has already been stated. However, the opportunity to compare the effect of penicillin with that of antitoxin in cases No. 1998 and 1997 was a fortunate one, and the group of cases selected provided a test of the ability of penicillin to alter the course or prevent death in subacute but severe tetanus.*

It is possible that the failure of penicillin in this series was due to inadequate dosage or failure to maintain a blood level throughout the 24 hours. The lack of facilities for determination of blood level and for *in vitro* testing of bactericidal action was a serious hindrance to the study. In the future consideration should be given to possible effects of large booster doses such as have been used in subacute bacterial endocarditis.⁹ Further controlled investigation, including trial with various fractions not always present in

* An interesting experiment which is to be submitted for publication by 1st Lt. Dwight L. Lichty, VC, AUS, of the 145th Veterinary Food Inspection Department, was brought to the writer's attention by personal communication. Lt. Lichty had the opportunity to treat a horse afflicted with tetanus on the first day of development of symptoms. The animal was seen at the Taira Military Government corral because of a puncture wound which occurred on September 19, 1945. The horse was small, weighing only 600 lb., but was in generally good condition. The puncture wound was located just below the stifle, right anterior. Ten days after injury, on September 29, 1945 tetanus was manifested by a saw-horse stance, extended neck, rigidity of the legs and early trismus. Loud noise produced slight muscular spasm and complete contraction of nictitating membranes. The horse was placed in a sling. Nutrition was maintained by tube feeding as well as voluntary eating during periods of relaxation. Barbiturates and chloral were used in maximum doses to effect sedation and muscular relaxation. Tetanus antitoxin was not employed.

Penicillin in doses of 100,000 units each was administered every three hours for 90 hours. (The recommended dose for an average size horse in treatment of susceptible infections is 50,000 units every three hours). Of the 30 original doses, three were given intrathecally, the others intramuscularly. After the ninetieth hour 50,000 units were injected intramuscularly every three hours through the one hundred and thirty-eighth hour. One million units was given each 27 hours during the first 30 injections. The total penicillin administered was 4,100,000 units.

During the course of this treatment the animal showed persistent and complete trismus and failed to respond to therapy. It died on the morning of the eighth day, approximately 170 hours after the onset of therapy.

This interesting clinical trial is important because the amount of penicillin administered was twice the recommended therapeutic dosage. It was possible to give injections every three hours and thus presumably to maintain a satisfactory blood level. Treatment was instituted at the earliest possible moment, and no therapy other than sedatives was given.

commercial penicillin, is warranted before arriving at final conclusions, especially in view of the laboratory reports of in vitro inhibition of *Clostridium tetani* already referred to above.

SUMMARY AND CONCLUSIONS

1. Fifteen cases of tetanus of three to 11 days' duration were treated by intramuscular injection of penicillin in doses of 20,000 units every four hours with the exception of the interval 2200 to 0600. Most of the patients received a total of 500,000 units or more. One patient was given 150,000 units in injections about her wounds.

(a) Of this group seven patients recovered, three (including the patient injected locally) improved, and five died. In none of the cases treated was there observable alteration of the course of tetanus which seemed attributable to the use of penicillin. Wound infections were generally benefited, and the indication for use of the drug in complicating infection is clear. However, there was no tendency toward reduction of mortality in severe tetanus and no improvement in cases which had failed to respond to antitoxin. Recovery and improvement were gradual in the cases which survived, and the clinical course was comparable to that in other cases which recovered after only prophylactic doses of antitoxin or without any treatment whatever.

2. Four patients who had received or who were given known amounts of antitoxin were observed under conditions identical with those of the penicillin group. These patients showed a striking clinical change after administration of antitoxin. One of the four was comparable in many respects to a patient treated with penicillin, and the favorable response to antitoxin was in sharp contrast to the failure of penicillin to affect the course of the disease.

3. Twenty-seven patients on general service who had received undetermined amounts of antitoxin were observed during the 18 day period of investigation. Of these patients, most of whom had been given small and presumably inadequate amounts of antitoxin, 16 made complete recoveries, seven others improved and three died. One patient declined progressively and probably terminated fatally.

4. The relatively high mortality in the first group was attributable largely to the selection of patients with severe tetanus in order to test the possible efficacy of penicillin. It would obviously have been difficult to evaluate a drug in a series in which recovery would have been anticipated under any type of therapy.

5. On the basis of this study there are no indications that commercial penicillin is an effective agent in the treatment of tetanus. In vitro evidences of antibacterial action are not supported by clinical indications of a similar effect in vivo. The possibility is mentioned that other penicillin fractions or larger doses may be effective.

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THE PREPONDERANCE OF RIGHT HYDROTHORAX IN CONGESTIVE HEART FAILURE *

By EDGAR M. McPEAK, M.D., F.A.C.P., *Houston, Texas*, and SAMUEL A.
LEVINE, M.D., F.A.C.P., *Boston, Massachusetts*

ALTHOUGH there has been a strong clinical impression that right hydrothorax is more common than left hydrothorax when gross congestive heart failure occurs, recently this point of view has been questioned. In a survey by Bedford and Lovibond,¹ these authors were led to the conclusion that although right hydrothorax was more common in cases showing mitral stenosis, combined right and left heart failure and auricular fibrillation, the occurrence of left hydrothorax was favored by hypertension, left heart failure and normal rhythm. Owing to the strong impression we have had that right hydrothorax was much more common in congestive heart failure, regardless of the underlying cause, the following study was made to determine the actual facts. Consecutive cases of congestive heart failure showing hydrothorax were selected, after eliminating those presenting extraneous factors, such as pleurisy with effusion, active rheumatic fever, significant nephritis, blood dyscrasias, neoplasm, hepatic disease, etc. The purpose of this was to include for consideration only those suffering from clear-cut cardiovascular disease with congestive failure.

The first method of approach was to review 75 clinical cases of congestive heart failure that required thoracentesis. In each case the side of the chest tapped was the only one in which fluid appeared to be present or was the one that seemed to show the larger degree of hydrothorax, where some disproportion in the two sides existed. This decision was made by the ordinary methods of bedside examination with or without the aid of roentgen-ray. The second analysis consisted of comparing the roentgen-ray findings in 52 consecutive cases of congestive heart failure with hydrothorax. In no instance had thoracentesis been performed in this group, and the relative degree of hydrothorax on the two sides was estimated by the roentgenologist. The basis of the third study consisted in determining the amount of fluid in the two pleural cavities in 110 cases of congestive heart failure that came to postmortem examination. The above three analyses ought to serve as controls for each other and should give convincing evidence if they all agree in their conclusions.

Of the 75 cases of hydrothorax requiring thoracentesis (table 1), 35 had rheumatic heart disease, 22 had a significant degree of coronary sclerosis and 18 had hypertensive heart disease. Owing to the tendency for hydrothorax to recur following thoracentesis, no more than two chest taps from

* Received for publication March 13, 1946.

From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School, Boston.

TABLE I
Hydrothorax in Congestive Heart Failure, Thoracentesis

Heart disease		Rheumatic	Coronary	Hypertensive	Total
Site of hydrothorax	R*	28	16	11	55
	L	3	1	4	8
	B	4	5	3	12
Total cases		35	22	18	75
Site with auricular fibrillation	R	20	4	1	25
	L	1	0	1	2
	B	(R>L) 1	2	0	3
		(L>R) 2	0	0	2
Chest taps	R	45	22	14	81
	L	4	2	4	10
	B	(R>L) 2	5	3	10
		(L>R) 2	0	0	2
Total taps		57	34	24	115
Average amt. fluid removed	R	1000 c.c. (45)	1050 c.c. (22)	1050 c.c. (14)	1050 c.c.
	L	1100 c.c. (4)	1050 c.c. (2)	1000 c.c. (4)	1050 c.c.
	BR	1100 c.c. (4)	1300 c.c. (5)	1200 c.c. (3)	1200 c.c.
	BL	1150 c.c. (4)	550 c.c. (5)	800 c.c. (3)	850 c.c.

* R = right, L = left, B = bilateral, BR = bilateral R>L, BL = bilateral L>R.

any one case were included in this study, regardless of whether both were performed on the same side or one on each of the two sides. Auricular fibrillation was present in 32 of this series of cases, 24 being in the rheumatic group, six in the coronary and only two in the hypertensive group. Twenty-five of these 32 cases were aspirated from the right chest only, two from the left chest alone and in five bilateral taps were done with a greater amount of fluid removed from the right cavity in three of these. In the rheumatic group 57 thoracenteses were performed on the 35 cases, 49 times on the right side and eight times on the left. In 45 instances the right chest alone was aspirated and in only four the left alone. There were four instances in which both sides were tapped. It is of interest that the amount of fluid removed at each thoracentesis was almost the same no matter which side was tapped. When a similar review was made of the 22 cases of coronary heart disease it was found that 34 chest taps were performed, 27 on the right side and seven on the left, 22 on the right side alone and two on the left alone. In five instances bilateral paracenteses were done although in each instance the right hydrothorax was greater than the left. It seems significant that

while the average amount of fluid aspirated, where only one side was explored, was 1050 c.c., in the five cases in which both sides were explored an average amount of only 550 c.c. was obtained from the left side and 1300 c.c. from the right. In the last group, consisting of 18 cases of hypertensive heart disease, 24 chest taps were performed, 17 on the right and seven on the left, 14 on the right side alone and four on the left alone. Three bilateral aspirations were done, and in each instance the amount of fluid removed from the right pleural sac was greater than that removed from the left, the average being 1200 c.c. from the right and 800 c.c. from the left. In summary, among the 115 thoracenteses performed on 75 cases of congestive heart failure, 93 were done on the right chest and 22 on the left, 81 on the right chest alone and 10 on the left alone. In the 12 instances where both sides were explored, only twice was the amount of fluid removed from the right side found to be less than that removed from the left side.

The second approach toward determining the distribution of hydrothorax was made on 52 consecutive cases which had had no previous thoracenteses and were analyzed from the roentgenological evidence alone (table 2). Of this group the 18 with rheumatic heart disease presented pure right hydrothorax in nine instances, pure left hydrothorax in three, and in six fluid occurred bilaterally and about equally on the two sides. In the 12 cases of coronary artery disease, right unilateral hydrothorax was present in three, and in the other nine fluid was present on both sides, predominantly right in four, predominantly left in two, and about equally in three. The 16 cases of hypertensive heart disease showed fluid in the right thorax only in six, and all the remaining presented fluid bilaterally, more on the right in four, more on the left in two, and about equally in four. No definite tendency

TABLE II
Hydrothorax in Congestive Heart Failure, Radiological Examination

Heart disease		Rheumatic	Coronary	Hypertensive	Misc.	Total
Site of hydrothorax	R	9	3	6	2	20
	L	3	0	0	1	4
		(R>L) 0	4	4	1	9
	B	(R=L) 6	3	4	1	14
		(L>R) 0	2	2	1	5
	Total	18	12	16	6	52
Site with Aur. Fib.	R	5	1	2	0	8
	L	1	0	0	0	1
		(R>L) 0	1	0	1	2
	B	(R=L) 4	1	1	0	6
		(L>R) 0	0	0	1	1

to a preponderance of fluid in either side of the thorax occurred in six cases of miscellaneous types of heart disease. Thus, of this entire series, 20 cases evidenced pure right hydrothorax, four pure left, with the remaining 28 presenting fluid on the two sides about equally, i.e. predominantly right in nine, predominantly left in five, and with no discernible difference in 14. Auricular fibrillation was present in 18 instances and of these 10 showed more fluid in the right chest, two in the left and in six it appeared to be equal. Unilateral hydrothorax in this group occurred approximately five times more often on the right side than on the left, and when the hydrothorax was bilateral there appeared no definite tendency for either side to predominate.

In the third study, 110 cases of congestive heart failure presenting hydrothorax at postmortem examination were analyzed (table 3), and the deductions were based on the amounts of fluid determined by direct measurement. It was realized that the agonal state might influence the formation of a terminal hydrothorax of limited degree, when the circumstances were favorable to such, and transudates of less than 300 c.c. were arbitrarily excluded from the study. A considerable number of these cases had had thoracenteses performed prior to death, and a quantitative analysis of the fluid so removed has been compiled for consideration.

The rheumatic group presented unilateral right hydrothorax twice, unilateral left three times, and in 50 the fluid was distributed bilaterally with the greater amount on the right in 44, on the left in four, and in two equally. In two of the three instances in which fluid occurred on the left side alone there was complete obliteration of the right pleural cavity by fibrous adhesions. Signs of left heart failure had dominated the clinical picture in five of the 55 cases, and in one of these fluid was found only on the left side, while on the other four it occurred bilaterally and predominantly right (3) or equal (1). Pulmonary infarction was present in 25 of this group and complicated left hydrothorax in three instances and right hydrothorax in one. In 21 cases so complicated, fluid was found in both cavities with the greater amount in the right in 20 of these. Prior to death auricular fibrillation had existed in 38 of the rheumatic patients, and of this number one showed fluid on the right side alone at autopsy, two on the left side alone and 35 presented fluid bilaterally with that on the right predominating in 33. The average amount of fluid found in the right pleural sac, in this rheumatic group, was 550 c.c. and that in the left sac was 350 c.c. Of similar interest is the fact that in 27 of this group of 55 cases, in which 73 clinical thoracenteses had been performed (57 right, 16 left), an average amount of 900 c.c. of fluid had been removed from the right thorax and 700 c.c. from the left thorax.

In this study, 25 cases of coronary heart disease presented hydrothorax entirely on the right in two instances, entirely on the left in one and in 22 it was bilateral with the right side predominating in 18, the left in three, and neither in one. Fibrous adhesions had completely obliterated the right pleural cavity in the one instance in which the fluid was limited to the left side. Nine of the 25 cases had presented the usual signs of marked left heart

TABLE III
Hydrothorax in Congestive Heart Failure, Post Mortem

Heart disease		Rheumatic	Coronary	Hypert.	Luetic	Total
Number		55	25	23	7	110
Average age		46	66	61	53	54
Site of hydrothorax	R	2	2	1	1	6
	L	3	1	1	0	5
		(R>L) 44	18	18	5	85
	B	(R=L) 2	1	0	0	3
		(L>R) 4	3	3	1	11
Site with lt. ht. failure	R	0	0	0	1	1
	L	1	1	1	0	3
		(R>L) 3	5	9	3	20
	B	(R=L) 1	1	0	0	2
		(L>R) 0	2	2	1	5
Site with pul. infarction	R	1	0	0	0	1
	L	3	0	0	0	3
	B	(R>L) 20	6	3	2	31
		(R=L) 1	0	0	0	1
Site with aur. fib.	R	1	0	0	0	1
	L	2	0	0	0	2
		(R>L) 33	4	3	0	40
	B	(L>R) 2	0	1	0	3
Average of fluid at PM	R	550 c.c.	550 c.c.	Above three groups considered together.		
	L	350 c.c.	400 c.c.			
Fluid removed during life	Cases	27	26			
	R	57	34			
	Taps					
	L	16	6			
Av	R	900 c.c.	950 c.c.			
	L	700 c.c.	900 c.c.			

failure before death, and of these one was the case of unilateral left hydrothorax, while the remainder showed fluid bilaterally, with that on the right predominating in five and that on the left in two. In six cases in which pulmonary infarction accompanied the hydrothorax the latter was found to be bilateral and predominantly right in all. Four of this group had had auricular fibrillation, and in all these the hydrothorax was also bilateral with the greater amount of fluid on the right side.

In 23 cases of hypertensive heart disease unilateral hydrothorax occurred only in two instances, once on each side, while bilateral hydrothorax occurred 21 times, in greater degree on the right in 18 and on the left in three. The right pleural space was completely obliterated by fibrous adhesions in the one case showing fluid on the left side alone. Signs of left heart failure had been the outstanding clinical features in 12 of the 23, and all these, except the case of left hydrothorax, presented fluid bilaterally with the greater amount in the right pleural cavity in nine, and in the left in two. In three cases where pulmonary infarction occurred the hydrothorax was bilateral and predominantly right sided in all. Auricular fibrillation had been present in four cases, and the hydrothorax was bilateral in all these, with that on the right greater in three.

Seven cases of syphilitic heart disease presented pure right hydrothorax in one, and in the other six it was bilateral, and predominantly right in five. Left heart failure had been outstanding in five of this group with one showing unilateral right hydrothorax and four showing fluid bilaterally with the greater amount on the right in three. In two cases evidencing pulmonary infarction the hydrothorax was bilateral and greater on the right side.

Because left heart failure had been clinically prominent in a relatively high percentage of the 55 cases, including the coronary, hypertensive, and syphilitic heart disease groups, these were conveniently considered together in calculating the average amount of fluid found in the two pleural sacs. Here again it was observed that the average amount of fluid found in the right sac (550 c.c.) exceeded that found in the left (400 c.c.). Likewise, 26 of these 55 cases had had 40 clinical paracenteses performed, 34 on the right chest and six on the left chest, with the removal of an average amount of 950 c.c. fluid from the right pleural cavity and 900 c.c. from the left.

This entire group of 110 cases of congestive heart failure, studied post mortem, presented hydrothorax on the right side alone in six instances, on the left side alone in five, and bilaterally in 99 or 90 per cent of cases. Of the latter there was found a greater amount of fluid in the right cavity in 85, more in the left cavity in 11 and in three it was equal. Complete obliteration of the right pleural space by fibrous adhesions could account for three of the five cases of pure left hydrothorax. It was thought that an extensive fibrous pleuritis, especially involving the lower portion of these membranes, might have influenced the distribution of the accompanying hydrothorax in 19 other instances, with involvement of the right pleura nine times, of the left three times, and of both right and left seven times. Only in rare instances did

such extensive pleural involvement suggest its presence either clinically or radiologically. Left heart failure had dominated the clinical picture in 31 cases. Among these the hydrothorax was unilateral and right in one instance, unilateral and left in three, and in the remaining 27 it was bilateral with the greater degree on the right in 20, on the left in five and in two it was equal. Recent pulmonary infarction had occurred in 36 cases, often presenting multiple areas, either unilateral or bilateral. In this group hydrothorax occurred on the right side alone in one instance, on the left alone in three, and bilaterally in 32 with a greater amount of fluid found in the right cavity in 31. In only rare instances did any close relation between the occurrence or distribution of hydrothorax and the presence of an infarctive process suggest itself. However, owing to the nature of the fluid, such cases might easily have been excluded from this study. In 1935 Joly² gave careful attention to this question and felt that pulmonary infarction seldom causes the formation of an extensive cardiac hydrothorax. Auricular fibrillation had been present in 46 cases, of which hydrothorax was limited to the right side in one, to the left side in two, while in 43 it was bilateral and predominantly right in 40. Although the percentage of occurrence of bilateral hydrothorax in this study was quite high, it would appear that the preponderant involvement of the right pleura was consistently evident regardless of the manner in which the cases were grouped for consideration.

The present observations and studies have led to findings which strongly support the general opinion in regard to the distribution of hydrothorax in congestive heart failure. Thus, when an analysis based on the incidence of thoracenteses was made, a marked tendency for the right chest to predominate the picture was encountered (table 1). In this series of cases one side of the chest was aspirated alone in 91 instances, 88 per cent being performed on the right thorax. When the hypertensive patients were considered as a group, the right thorax was aspirated in 71 per cent of instances. While this tendency was maintained, regardless of the underlying heart condition, it would appear that auricular fibrillation and other factors incident to rheumatic heart disease further favor a preponderance of right hydrothorax. In the second series of cases (table 2) as viewed by the roentgenologist, a greater amount of fluid was observed in the right pleural cavity in 56 per cent of instances and in 27 per cent it appeared to be about equal on the two sides. Although the number of cases considered here was quite small, there again appeared augmented influences favoring right hydrothorax in the rheumatic group. Published statistics on the distribution of hydrothorax, as determined at postmortem examination, appear to be in close agreement; however, the present series (table 3) indicated a greater percentage of bilateral hydrothorax than had been previously reported. This discrepancy may be partially accounted for by the manner of screening the subjects and by the use of different methods of recovering and considering the fluid. In 107 of this series of cases the amount of fluid removed from the right pleural cavity exceeded that removed from the left in 85 per cent.

This ratio varied between etiological groups, being found highest in the rheumatic and lowest in the syphilitic, but in no instance did it fall below 80 per cent. These studies indicate that from whatever angle an analysis is attempted, regardless of the method of approach or the underlying cardiac condition, the combination of factors which determine the transudation of fluid into the pleural sacs exerts an influence in such a manner as predominantly to involve the right pleura. This influence, however, appears to become augmented in rheumatic heart conditions as compared to those in which failure of the left heart is more frequently encountered.

DISCUSSION

When one attempts to review the numerous efforts that have been made to explain the distribution of hydrothorax which occurs in the course of congestive heart failure, one is struck by the fact that the subject has been approached from isolated points of view. This has led to an over-emphasis of some particular factor involved and a tendency toward over-simplification of the problem as a whole. Much of the work published has been based on clinical observation of the condition with theoretical conclusions drawn as to the most likely factor determining the distribution of the fluid. In 1867 Bacelli³ advanced the azygos theory to explain the comparative frequency of right hydrothorax, assuming that pleural fluid accumulated through disturbance in the systemic circulation. His views seem to have been accepted without question until the turn of the century and indeed have made themselves felt until much more recently. In 1904 Steele,⁴ reviewing his earlier work (1896) and that of Stengel,⁵ reported the occurrence of right hydrothorax alone, or as greater than left, in 60 per cent of clinical cases and in 77 per cent of those observed at postmortem examination. He and Stengel felt that pressure on the root of the right lung and azygos vein by an enlarged right auricle could explain the predominance of right hydrothorax and suggested that the site of a hydrothorax was associated with a corresponding enlargement of the right or left side of the heart.

Crediting West⁶ with having expressed similar views previously, Fetterhoff and Landis⁷ in 1909 presented a convincing argument that transudation of fluid into the pleural sacs took place from the visceral rather than the parietal layer and therefore depended upon involvement of the pulmonary instead of the systemic circulation. They argued that pressure on the right or left pulmonary veins, by a dilated right or left auricle respectively, determined the location of the pleural transudate. Since the right auricle was more easily and consequently more commonly dilated than the left, a predominance of right hydrothorax might be expected.

More recently (1930) Satke⁸ presented experimental data demonstrating a greater relative degree of pressure negativity in the right pleural space, as compared to that in the left, in normal individuals, and suggested this difference would explain the prevailing tendency toward preponderance of

right hydrothorax. This tendency was supported by Famulari⁹ on the basis of the anatomical relations existing between the thoracic aorta and the hemiazygos vein and the presence of valves in the latter. Dock¹⁰ in 1935 presented convincing evidence that the anatomic and hydrostatic factors relating to the flow of blood from the pulmonary venous bed to the left ventricle strongly favored the predominance of right over left hydrothorax. He pointed out these factors as being considerably augmented by the right lateral decubital position which cardiac patients generally prefer, according to the studies on "trepopnea" by Wood, Wolferth and Terrell.¹¹

Fishberg¹² states that although cardiac hydrothorax is often unequal and usually right sided, no adequate explanation has been given to account for this distribution. He expresses the opinion that transudation into the pleural sacs, due to heart failure, depends upon disturbance of the systemic as well as the pulmonic circulation. In studying left heart failure, Bedford¹³ found left hydrothorax in 18 of 38 cases, whereas fluid occurred on the right side alone in only nine instances. Because of the unusual incidence of unilateral left hydrothorax in this series, in opposition to accepted views, Bedford and Lovibond (1941) did a follow-up study including all types of congestive heart failure.¹ They agreed with Steele's earlier idea that there existed a definite relation between the underlying heart condition and the site of the hydrothorax and reached conclusions to which reference has already been made. It is of interest that Weiss¹⁴ in his studies of pulmonary edema found that usually congestion and edema started in the right lung and remained more intense on this side than on the left.

The relative rôles played by the systemic and pulmonary circulations in the pathogenesis of cardiac hydrothorax has been a subject of much speculation and controversy. With the accumulation of clinical and experimental data, however, there seems little doubt that the visceral pleura is to be considered the source of such fluid collections. Graham¹⁵ in 1921, working on the edematous lung excised immediately post mortem, was able to demonstrate the transudation of fluid from the visceral pleura by varying the degree of pressure negativity within the range of normal. He was convinced that the increased pressure negativity produced by forcible inspiration could suck excess fluid through the surface of the lung. Zdansky¹⁶ expressed the view in 1929 that, on the basis of radiological evidence, hydrothorax should be considered as the sequence of pulmonary engorgement and edema. Extensive observations were reported by Yamada¹⁷ in 1933 on several hundred presumably healthy Japanese soldiers, in whom pleural fluid could be aspirated in 29 per cent, and following severe exercise in 70 per cent of the same group. One wonders whether a heightened negative intrathoracic pressure, acting alone, could account for such unusual findings. The amounts of fluid dealt with were too small to warrant an opinion as to its actual distribution.

That almost the entire capillary venous return from the visceral pleura is received by the pulmonary veins has been shown by Miller¹⁸ in 1937.

More recently Drinker,¹⁹ in his noted lectures on pulmonary edema and inflammation, tersely stated, "It is generally acknowledged that two factors are fundamental in causing transudation in the lungs and pleural sacs. They are, first, sustained increase in pulmonary pressure, and second, anoxia—while one or the other may be dominant in a given case, they never, in my opinion, work alone." After discussing the variation, from tissue to tissue, in increased capillary permeability due to anoxia and emphasizing the particular vulnerability of the lung capillaries to this and other influences, he further stated, "It is my belief, I cannot say conviction—that simple pulmonary edema and the more serious pulmonary exudations depend more upon alterations in the permeability of the lung capillaries than upon complicated pressure relations in the pulmonary circulation."

Accepting the view that the visceral pleura is the principal source of abnormal collection of fluid within the pleural sacs, and owing to their peculiar environment, their increased susceptibility to anoxia, and the inadequacy of pulmonary lymph flow under stress,¹⁹ that the pulmonary capillaries are particularly vulnerable to the forces promoting transudation, there are yet to be considered a number of anatomical and physiological factors which may determine, modify, or tend to localize such a process.

A number of these factors pertain to the lungs themselves. The right lung is some 10 per cent greater in volume than the left and, considering the extra lobe on the right, the disproportion between the areas of visceral pleura on the two sides is even greater. Diseases of the lungs or pleurae, active or healed, were considered by Zdansky¹⁶ and Weiss²⁰ to influence the localization of pulmonary edema and therefore its sequelae. Pleural adhesions may influence the accumulation of pleural fluid either positively or negatively, depending upon the extent of the involvement. Christie and Meakins²¹ in their studies on intrapleural pressure changes in congestive heart failure, were able to demonstrate marked decrease in distensibility and impairment in elasticity of the lungs. Working along similar lines, Prinzmetal and Kountz²² considered the occurrence of a vicious circle in the relation of pulmonary congestion to lung ventilation. Any factor then, which tends to limit respiratory excursion, such as hypostasis, hepatic engorgement, cardiac enlargement, etc., tears down the natural defenses against the consequences of local increased capillary transudation.

It is difficult to visualize local pressure effects on the pulmonary venous return by an enlarged right or left auricle. There seems to be no consistent relation between such enlargement and the site of a hydrothorax from the radiologic point of view. Of greater significance may be gross cardiac enlargement resulting in direct compression of lung tissue. It is clear that the onset of cardiac arrhythmia often initiates congestive failure, but the high incidence of right hydrothorax in the presence of auricular fibrillation, as brought out by Bedford and Lovibond, warrants further study. The pulmonary lymphatic drainage, as shown experimentally by Warren, Peterson and Drinker,²³ takes place almost entirely through the right lymphatic

duct with limited anastomosis to the thoracic duct. One wonders what effect this might have on the lungs individually when lymphatic stasis occurs and whether the left lung receives greater benefit from the collateral drainage. The elective position patients assume, as emphasized by Dock²⁴ and by Wood et al., further influences capillary leakage and lymphatic stasis as does also the anatomic and hydrostatic factors described by Dock. That a single factor, such as thrombosis of a blood vessel or obliteration of a pleural space, can explain the location of a pleural transudate is clearly understood, but such instances are relatively rare.

It is much more difficult to form an impression as to the relative importance of the parts played by the visceral and parietal pleurae in absorption of fluid, and little experimental work seems to have been done on which to base an opinion. That the visceral pleura is active in the absorption of fluid is apparent in instances of localized interlobar pleural effusions. It is reasonable to regard the mechanism of pleural fluid formation as one in which there is constantly a transudation and reabsorption of fluid in the pleural sac. When excessive amounts are present either or both factors may be disturbed and recovery take place when the normal balance is reestablished. In consideration of the problem it would seem advisable to keep the fundamental factors of transudation in the lungs and pleural sacs in mind and to realize that in a given case a number of influences may be active together in determining the site of fluid accumulation.

SUMMARY AND CONCLUSIONS

1. The distribution of hydrothorax in congestive heart failure was determined in three groups of patients by three methods respectively, i.e., by thoracentesis, by radioscopy, and at autopsy.
2. The findings obtained from these three analyses were in close general agreement throughout the study.
3. Depending on the method considered, right hydrothorax predominated in from 56 to 80 per cent of cases and left hydrothorax in from 12 to 17 per cent. Fluid was equally distributed in 3 to 27 per cent.
4. When etiological groups of heart disease were considered, the predominance of right hydrothorax over left was maintained regardless of the underlying heart condition.
5. Rheumatic heart disease and auricular fibrillation appeared to augment the influences determining a right hydrothorax, while pure left heart failure tended to mitigate these to a limited degree.
6. Any explanation for the distribution of hydrothorax in congestive heart failure may be attempted only through consideration of a number of influencing factors. However, it is clear that the balance of these forces is exerted in such a manner as greatly to favor the involvement of the right pleural sac.

Recognition is given to Dr. M. C. Sosman for the radiological observations included, and to Drs. C. S. Burwell and C. K. Drinker for their kind advice and criticism.

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THE MECHANISM AND PREVENTION OF CARDIO-VASCULAR CHANGES DUE TO INSULIN *

By RICHARD A. GILBERT, 1st Lieut., M.C., A.U.S.,† and JOSEPH W. GOLDZIEHER, M.D.,‡ *Durham, North Carolina*

ASIDE from troublesome hypoglycemic reactions insulin is generally considered a rather innocuous drug in therapeutic dosage. Joslin¹ and others² have alluded to dangers of insulin therapy in patients with cardiac disease, but very little attention has been paid to these warnings, and insulin is often dispensed to older diabetics in a care-free and almost routine fashion. Büdingen,³ von Noorden⁴ and others were impressed even at an early period by dangerous and sometimes fatal cases of anginal syndrome following insulin therapy in aging diabetics. Gigon⁵ reported the sudden death of a diabetic with heart disease after the third injection of insulin. Schönbrenner⁶ described severe electrocardiographic changes in a diabetic with heart disease, who had been treated with insulin for four days and whose blood sugar was 229 mg. per cent when these changes were present. Joslin⁷ reported a patient admitted in insulin shock, who on autopsy a few days later was found to have a fresh myocardial infarction. Within the past year we have observed three cases of acute myocardial infarction (confirmed at autopsy) which occurred immediately following an episode of hypoglycemia induced by insulin therapy in diabetics with atherosclerotic heart disease. The frequency of heart disease and its complications in diabetes mellitus is common knowledge, but one might be inclined to suspect the possible rôle of insulin as a factor in the high incidence of angina pectoris or coronary occlusion, which is five times as common in diabetics as in nondiabetics of the same age.⁸

Following the widespread use of insulin shock in the treatment of schizophrenia, further indications of the dangers of insulin therapy have become apparent. Schou⁹ reported 13 cases of serious cardiac complications in 375 patients treated with insulin shock. Gralnich¹⁰ described a patient who developed pulmonary edema and electrocardiographic changes resembling coronary occlusion during insulin shock. Others^{11, 12, 13, 14} emphasized circulatory changes as a danger of insulin shock therapy. One observer¹⁵ found no electrocardiographic changes in nine patients treated with insulin or metrazol.

In order to investigate the relationship of insulin and cardiovascular changes, the following studies were undertaken on a total of 18 patients.

* Received for publication March 14, 1946.

From the Second Medical Division, City Hospital, Welfare Island, N. Y., Department of Hospitals, New York, N. Y.

† Now on active duty with the U. S. Army.

‡ Now at the Endocrine Division, Duke University Hospital, Durham, N. C.

EXPERIMENTAL STUDIES

Experiment 1. Eight patients were used in this group; three were young individuals (18 to 35 years) with no evidence of heart disease, and five were older individuals (over 50 years); of these, two suffered from severe anginal syndrome and three were in actual congestive failure at the time these experiments were performed. The patients were placed on a high carbohydrate diet for several days, and then three studies were carried

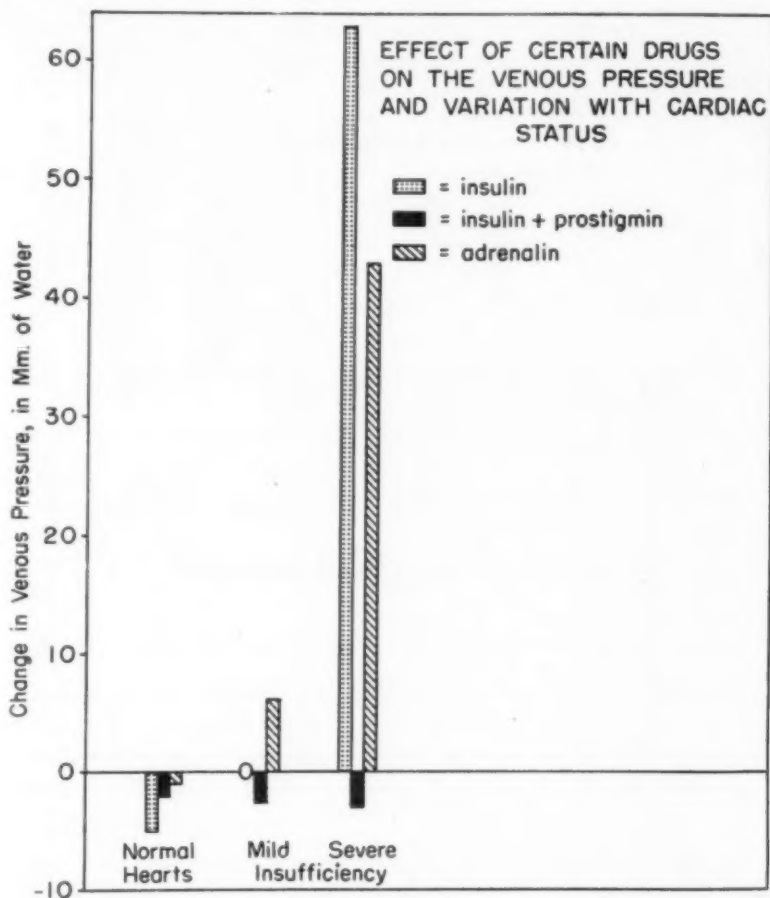


FIG. 1.

out on each one. First, 25 to 35 units (depending on the body weight) of regular insulin were given intravenously, and the blood sugar was allowed to fall to severely hypoglycemic levels (50 to 35 mg. per 100 c.c.). This state was maintained for two hours. On another day, each patient was given the same dose of insulin as before together with 1.0 mg. of prostigmin,⁵¹ and 15 minutes later 0.5 mg. of prostigmin was injected. On a third day each patient was given 10 minims of a 1:100 solution of adrenalin hydrochloride.

Control studies of respiration, blood sugar, blood pressure, pulse rate, venous pressure, ether and decholin circulation time, and electrocardiogram were made at the start and repeated every 15 to 30 minutes throughout the experiment.

Results. The effects of insulin and adrenalin on the blood sugar, blood pressure and pulse rate are too well known to deserve discussion; suffice it to say that our results were in full agreement with the established data.

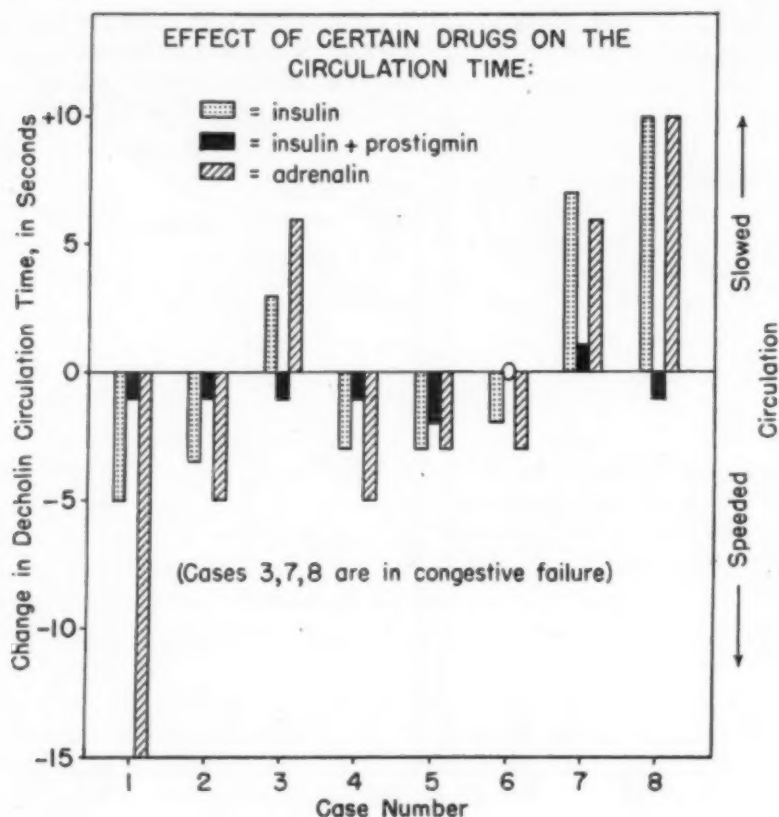


FIG. 2.

A. *Venous pressure.* The effect of these drugs on the venous pressure varied with the cardiac reserve as seen in figure 1. It is evident that in normal hearts and in hearts with mild diminution of the cardiac reserve, the changes were slight. In the severe cardiacs, however, profound and parallel alteration were induced by insulin and adrenalin. Prostigmin administered simultaneously with the insulin completely inhibited this change in all cases.

B. *Circulation time.* Figure 2 summarizes the data. Insulin hypoglycemia and adrenalin had essentially the same effect in every case, with the latter generally more effective. It is interesting to note that the circulation

was slowed only in those cases with congestive failure. Prostigmin counteracted the effect of insulin in every case, regardless of the direction of change.

C. *Heart rate.* Figure 3 shows a further effect of prostigmin. With insulin hypoglycemia, as with adrenalin, the heart rate rises gradually. The addition of prostigmin to the insulin not only prevented the increase in heart rate, but actually produced a slight bradycardia in most cases.

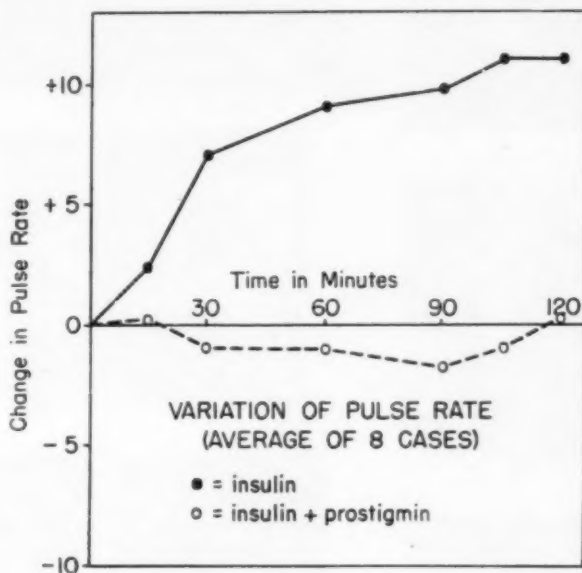


FIG. 3.

D. *Electrocardiographic changes.* In the three normal patients:

1. *Insulin alone* shortened the QRS interval once. ST was depressed once and the T-wave slightly depressed twice.
2. *Adrenalin* caused no appreciable changes.
3. *Insulin plus prostigmin* shortened PR once. There were no ST segment or T-wave changes.

In the group of five cardiacs, changes were far more pronounced.

1. *Insulin alone* lowered P twice, shortened PR twice. No widening of QRS, as seen by other investigators, was observed in our material. The ST segment was elevated in three cases and accompanied an inversion of T.

2. *Adrenalin* elevated the ST segment in two cases, depressed ST in one, and produced T inversion once. Aside from actual inversion of T, both insulin and adrenalin changed the upright T-wave to one more round-shouldered, symmetrically-limbed, simulating the type of change observed in coronary insufficiency (see figure 4). These alterations were produced in almost parallel fashion by insulin and adrenalin.

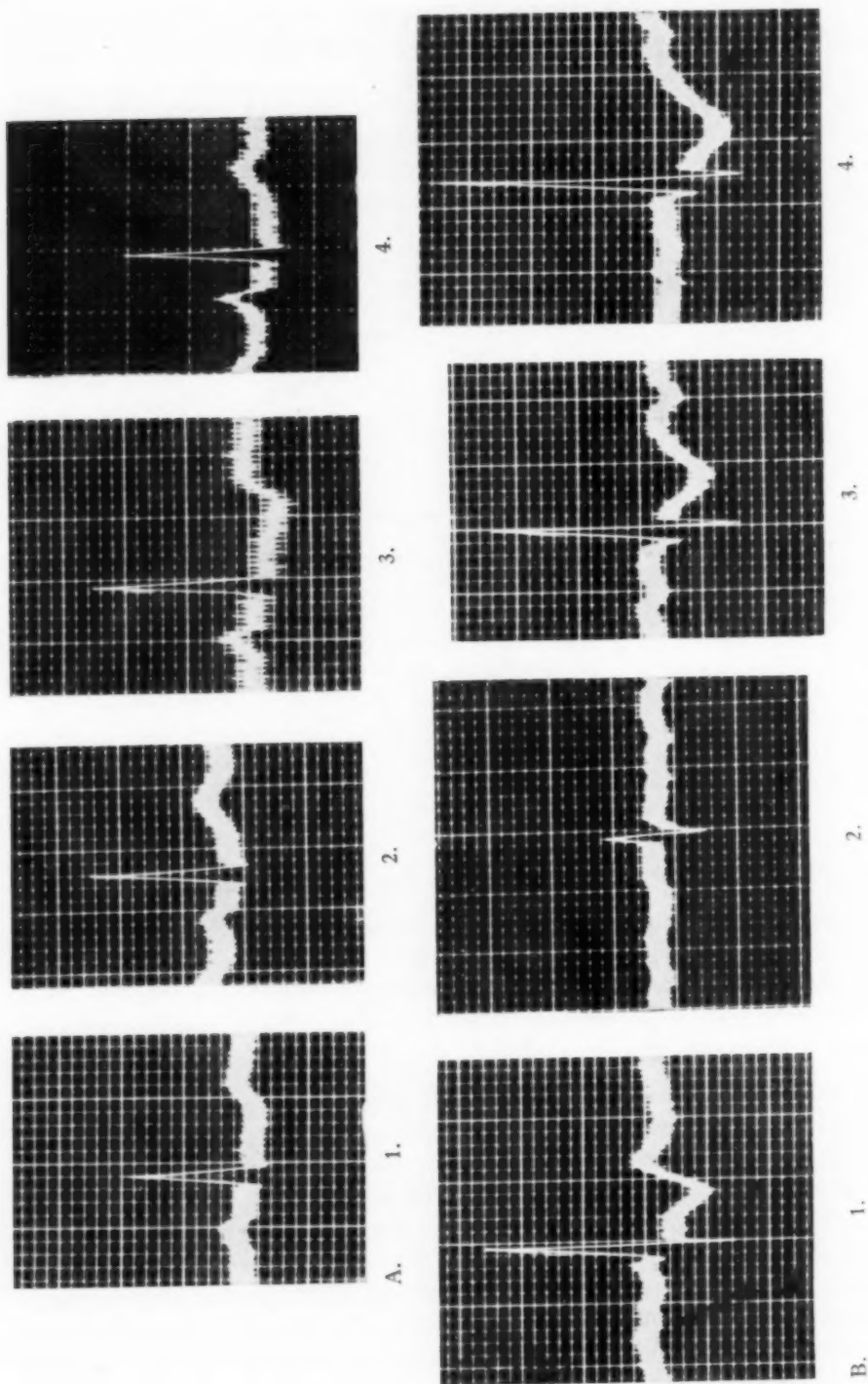


Fig. 4.

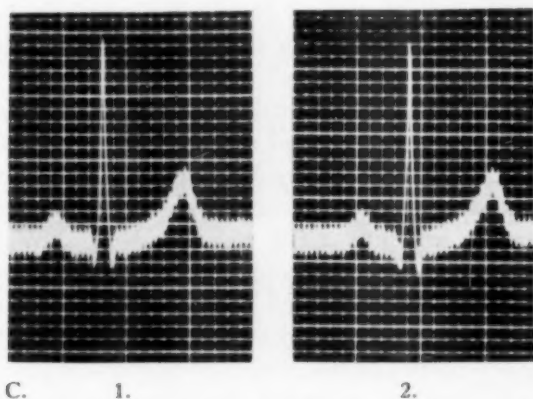


FIG. 4. *Experiment 1.* A: 1. Control EKG before insulin hypoglycemia. 2. During insulin shock. 3. Control EKG before adrenalin. 4. After adrenalin injection.

With insulin, observe: elevation of ST segment; T-wave becomes peaked, symmetrically limbed with round, sloping shoulders. Almost identical changes occur with adrenalin.

B: 1. Control EKG before insulin hypoglycemia. 2. During insulin shock. Control EKG before insulin-prostigmin. 4. During insulin-prostigmin hypoglycemia.

With insulin, observe: Decreased amplitude of QRS with more pronounced S-type configuration; elevation of ST segment; flattening of diphasic T-wave. Note that none of these changes appears during hypoglycemia following insulin-prostigmin.

Experiment 2. C: 1. Control EKG. 2. Two hours after insulin plus glucose (blood sugar level elevated 15 mg. per cent). No sympathetic stimulation. Observe that EKGs are identical.

3. *Insulin plus prostigmin* caused no alteration of the electrocardiogram in any instance.

Experiment 2. Five healthy young adults (18 to 35 years) and five older patients (over 50 years) with moderate or advanced diminution of cardiac reserve were used. After a control electrocardiogram, each patient was given a mixture of 25 U. regular insulin and 50 gm. glucose intravenously, as well as 400 gm. glucose in grapefruit juice by mouth. Serial electrocardiograms and blood sugar determinations were made for two hours.

Results. The amount of glucose administered maintained the blood sugar level at least 10 mg. per 100 c.c. higher than the starting level in every case. No tachycardia or other evidence of sympathetic stimulation was noted although these signs were watched for carefully. The results were uniform: in no instance did any electrocardiographic change occur within two hours following insulin injection. (See figure 4.)

DISCUSSION

In order to evaluate these experiments properly, a brief review of the background of this problem is necessary.

Pathology. In the course of their studies on insulin shock, Hadorn and Walthard¹⁶ investigated the effect of insulin on the rabbit's heart. The findings in 47 animals led them to conclude that neither single injections of insulin nor insulin shock produced any anatomically demonstrable injury

of the myocardial fibers. Meessen¹⁸ reported disseminated necroses of the myocardial fibers in rabbits surviving the injection of insulin for 24 hours. Negri¹⁷ found similar necroses as well as patchy or diffuse cellular infiltration in both insulin-treated and control animals; he ascribed these changes to an infection common in rabbits, and did not believe that they were in any way related to the treatment with insulin. Tannenberg¹⁹ investigated this problem in a somewhat different manner, giving animals repeated daily doses of insulin in varying amounts. The muscle fibers showed swelling and hydropic degeneration and there were localized vasodilatations and constrictions. No necroses or infiltration were found. Tannenberg's data indicate that these changes probably disappeared in two or three days. In view of the transitory nature of the electrocardiographic changes which have been associated with insulin treatment, it seems far more likely that any histologically demonstrable alteration of the muscle fibers would be of the reversible character that Tannenberg describes rather than irreversible necrosis or infiltration.

The Effect of Insulin Injections on the Circulatory System. Many investigators have studied the effects of insulin injections on the circulatory system.^{20, 21, 22, 23, 24, 25, 26} A tachycardia, appearing one-half to one hour after injection, has been observed uniformly. Changes in blood pressure were usually found, with a rise of the systolic and a fall of the diastolic pressure. Though both effects did not always occur together, an elevated pulse pressure resulted consistently. Venous pressure and venous oxygen content both increased. All investigators concurred in finding an increased cardiac output, stroke volume, or other index of increased cardiac work. Studies of the electrocardiographic changes have been equally numerous.^{13, 17, 20, 21, 24, 25, 30, 39} In man, arrhythmias and extrasystoles were uncommon. Generally a small P, widening of the QRS complex, depression of the ST segment and flattening or inversion of the T-wave appeared. Many investigators observed the lack of correlation between the blood sugar level and the electrocardiographic changes. One³⁰ described a patient who showed no clinical symptoms with a blood sugar of 52 mg. per 100 c.c. and whose electrocardiogram remained unchanged. Another¹⁰ reported a patient who showed changes simulating infarction during routine insulin shock therapy. Two investigators^{15, 24} saw no "important" electrocardiographic changes and one of these²⁴ found no persistent changes even after repeated episodes of insulin hypoglycemia.

Clearly, the circulatory system is intimately affected by the injection of insulin. The explanation of these phenomena is in many respects still obscure. In general, three theories have been offered for the action of insulin on the circulatory system:

1. The effects are due to hypoglycemia.
2. The effects are due to insulin itself.
3. The effects are due to adrenalin discharge and to stimulation of the sympathetic nervous system.

The Hypoglycemia Theory. The most obvious solution of this problem was to associate the lowered blood sugar with the cardiac manifestations. The diminution of the food supply of the heart muscle was generally thought to be an important factor.¹⁴ This belief was based on rather fragmentary knowledge of cardiac metabolism, as has been shown by Evans,²⁷ McGinty and Miller²⁸ and others. These authors have demonstrated that heart muscle does not utilize glucose directly, or does so to a minor extent. By contrast, the heart removes considerable amounts of lactate from the blood; pyruvate, β -hydroxy-butyric acid and certain fats can also be metabolized. Cardiac glycogen is apparently used only as an emergency substance or is normally replaced as fast as it is used up. Thus it would appear that there is not such a critical lack of cardiac fuel as was originally supposed. A second important point, one that has been observed by many investigators,^{13, 21, 28, 31} is that there is no correlation between the clinical picture and the blood sugar level. Moreover, the electrocardiographic changes are not necessarily reversed by glucose^{21, 31} and may even increase during subsequent hyperglycemia.²⁵ Perhaps the most conclusive proof was furnished by Costedoat and Aujaleu³² who found no electrocardiographic changes whatever in rabbits with severe hypoglycemia induced by phlorizin poisoning. Soskin and his coworkers³¹ found that electrocardiographic changes occur in eviscerated dogs when the blood sugar falls below 30 mg. per 100 c.c. It is doubtful if this observation has any direct bearing on the changes observed in man.

Costedoat et al.³³ also disproved the hypothesis that glycogen depletion of the heart muscle—which may occur during insulin hypoglycemia^{34, 35, 36}—is responsible for the electrocardiographic changes. Complete depletion of the cardiac glycogen was produced in rabbits by phlorizin without any corresponding alterations of the electrocardiogram.

The Insulin Theory. Various observations have been cited to prove that insulin has a direct effect on the heart. Citron³⁷ has demonstrated transitory electrocardiographic changes in the frog's heart perfused with insulin. The patient described by Schönbrunner⁶ (see above) has often been cited as proof. However, it must be pointed out that a blood sugar of 229 mg. per 100 c.c. at some time during insulin therapy does not preclude the possibility of previous unnoticed sympathetic stimulation. The persistence of electrocardiographic changes after the restoration of a normal blood sugar level does not prove a direct effect of insulin, but merely indicates that the electrocardiographic changes are not as rapidly reversible as the blood sugar level. Moreover, the electrocardiograms of Soskin et al.³¹ indicate that tachycardia—and possibly other evidences of sympathetic stimulation—were present. Von Haynal et al.²¹ claimed to have obtained electrocardiographic changes although the blood sugar level was maintained. Examination of the protocols reveals that the blood sugar was allowed to drop 20 mg. per 100 c.c. or even more before relatively scanty amounts (6.6 to 16.0 gm.) of glucose were given. Elevation of the pulse rate in several instances suggests strongly that the rôle of the sympathetic system was not excluded by

these experiments. When adequate precautions against this side-effect are taken, our findings indicate that no electrocardiographic changes appear.

Certain other properties of insulin have not heretofore been considered in relation to their cardiovascular implications. Insulin exerts a powerful tissue-hydrating effect, either directly or indirectly.^{38, 39, 40, 41} Excessive tissue hydration and interstitial edema are capable of producing both functional and electrocardiographic changes, as seen for instance in myxedema. Insulin also has a tendency to liberate intracellular potassium.³⁸ Chronic potassium deficiency produces cardiac failure⁴³ and myocardial changes due to potassium deficiency in man have been described.⁴⁴ However, adrenalin itself also liberates intracellular potassium.⁴² The importance of tissue hydration and cellular potassium depletion, whether produced by insulin or adrenalin, is still an unexplored question. It is entirely possible that certain persistent cardiac changes may be due to this factor. The short-term changes studied in our experimental material were readily inhibited by a parasympathomimetic drug (prostigmin), and hence do not require alterations of electrolyte metabolism for their explanation. That such changes may exist, however, is neither suggested nor negated by our material.

The Autonomic Theory. The brilliant work of Cannon and his group²⁹ has served to elucidate an extremely important factor in this problem. They found that insulin hypoglycemia was not accompanied by tachycardia or blood pressure changes in the experimental animal if the heart was denervated and the adrenals removed. Adrenalectomy without heart denervation did not abolish these changes, showing that the entire sympathetic (that is, adrenergic) system was involved. The sympathetic stimulation produced by hypoglycemia was promptly reversed by the intravenous administration of glucose.

Clinically, the symptoms of insulin hypoglycemia are strikingly similar to those following the injection of adrenalin, and this point has been emphasized repeatedly.^{45, 46} The final proof was supplied by Brandt and Katz⁴⁷ who demonstrated the presence of increased amounts of adrenalin-like substances in the blood during insulin hypoglycemia.

Hadorn¹³ has described inversion of the T-wave following the injection of adrenalin. Knowing the sympatholytic effects of ergotamine, Kugelmann²⁶ administered both ergotamine and insulin to animals and found that 40 per cent failed to show the usual vascular changes although the blood sugar was lower than that of the controls. On the other hand, both ergotamine¹³ and atropine³⁷ increase and prolong the electrocardiographic changes induced by insulin. The explanation and significance of these paradoxical observations is not clear at the present time.

From the literature we have summarized and from our own investigations it appears that the hypoglycemic theory of the insulin cardiac effects fails to account for the observed phenomena, except under the special circumstances of Soskin's experiment. Some investigators believe that the electrocardiographic changes are produced by insulin itself. As has been

shown, the evidence in the literature for this hypothesis is not convincing, and our studies fail to substantiate it in any respect. On the other hand, both the studies of other investigators and the material presented in this paper confirm the essential identity of the cardiovascular effects of insulin and the sequelae of sympathetic stimulation. It is most likely, therefore, that a drop in blood sugar induced by insulin elicits adrenalin discharge from the adrenal medulla as well as direct cardiac stimulation via the sympathetic nerves to the heart. Our findings show that prostigmin counteracts the effects of this stimulation; the mechanism of this effect is not entirely clear. Two possible explanations suggest themselves: first, that prostigmin prevents adrenalin production and second, that prostigmin prevents the normal cardiac response to adrenalin. Prostigmin simply inhibits the activity of cholinesterase; it is not known to interfere with the production of adrenalin. In fact the opposite may be expected in the presence of increased amounts of acetyl choline, upon which the production of adrenalin depends. The second possibility therefore seems more likely: the increased parasympathetic activity decreases the responsiveness of the receptor organ (i.e., the heart) to the presumably unaltered discharge of adrenalin and sympathin.

There exists some controversy over the significance of the ST and T-wave changes seen with insulin hypoglycemia. Some workers, citing their reversibility, minimize the importance of these alterations. Hadorn and others believe that they are to be considered as actual evidence of myocardial damage despite their reversibility. It must be pointed out that these changes are nonspecific; identical, transitory changes can be produced by temporary, mild anoxia in patients with even a minimal decrease of the cardiac reserve.⁴⁹ Far more important in our eyes is the indisputable fact that the sympathetic stimulation which evidently causes these changes also increases cardiac work—an obviously undesirable and potentially harmful feature. With the establishment of this fact, the question becomes more or less academic.

We believe that certain rather practical recommendations follow from these experiments. It seems to be clear that the harmful effects of insulin therapy—that is, the increased cardiac work—can be counteracted by prostigmin. It is possible that the routine combination of these two drugs would be of value in the treatment of diabetics with diminished cardiac reserve. The method of diabetic control advocated by Joslin and his school employs diets and insulin calculated with great exactitude. Whereas this method may be theoretically preferable and actually feasible in specially equipped institutions, it involves manifest hazards and practical difficulties in the vast majority of ambulatory diabetics. With the unpredictable variation in energy requirements due to environmental influences it is almost inevitable that the blood sugar level should vary sufficiently to produce compensatory sympathetic activity at some time. The undesirability of such a reaction, in view of the foregoing data, is obvious. In this respect, a method of diabetic control as suggested by Tolstoi et al.⁵⁰ appears distinctly

superior: carbohydrate in excess of the calculated requirement is permitted and there is no concern over the spillage of the excess sugar. With this method, there is far less chance for the development of hypoglycemic sympathetic stimulation.

SUMMARY

The effects of insulin on the heart rate, venous pressure, circulation time and electrocardiogram were investigated and found to be essentially identical with those of adrenalin.

The administration of insulin with the maintenance of an unlowered blood sugar and the absence of sympathetic stimulation produced no electrocardiographic changes. It follows that the changes observed with insulin alone are due to sympathetic stimulation secondary to the insulin-induced hypoglycemia.

Attention is called to the dangers of insulin therapy in patients with heart disease, as borne out by three personally observed and autopsied cases of acute myocardial infarction immediately following an episode of insulin hypoglycemia.

The cardiovascular effects of insulin injection may be counteracted by the simultaneous administration of prostigmin.

The possible advantages of combined prostigmin-insulin therapy in diabetics with diminished cardiac reserve are suggested.

We wish to acknowledge our indebtedness to Dr. Walter Bense and to Dr. Otto Loewi for their invaluable suggestions as to the presentation of this material.

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DICOUMAROL THERAPY *

By JOHN B. LEVAN, M.D., F.A.C.P.,† *Reading, Pennsylvania*

1. This study discusses the factors concerned with dicoumarol therapy.
2. The initial dosage and a practical way of estimating maintenance dosage are shown.
3. The daily plasma prothrombin times, factors affecting them, and the need for dependable laboratory technic are emphasized.
4. The variation in degree of response, the lag period, and the therapeutic level are discussed.
5. Hemorrhage, the only toxic manifestation of dicoumarol, is considered, and the methods of treatment are stated.
6. The contraindications are listed.
7. The results of therapy in 60 patients including 13 cases of pulmonary embolism are discussed.

The rationale for dicoumarol therapy is based on the pathology of thrombosis, thrombophlebitis, and embolism as set forth in numerous papers. The insidious development of venous thrombosis and its unpredictable behavior are the chief causes for controversy concerning their treatment.^{1,2} Frequently pulmonary embolism is the first sign of phlebothrombosis,³ and not uncommonly a day or two passes before signs and symptoms reveal its site. Here the clot is soft, friable, and poorly organized. It is easily detached from the vessel wall to float away in the venous current.⁴ Its highest incidence is in the calf muscles,⁵ although the feet, thighs, and pelvis may also be involved. The physically more impressive thrombophlebitis, as exemplified by "milk leg," is manifested by multiple signs and symptoms¹ and yet is the least dangerous of the clotting processes, for here the thrombus is organized and well attached. Only by extension and propagation does it offer a threat of embolism through formation of a fresh loose friable clot. One may surgically ligate the femoral vein to shut off this process, only to have it resume proximally.⁶ Where the site of thrombosis is not determined, one would be forced to do a bilateral femoral vein interruption. Studies have shown that patients over 40 years of age confined to bed for either surgical or medical reasons commonly have bilateral phlebothrombosis.⁷ In cases of pelvic phlebitis, surgical treatment is obviously impossible. Surgical ligation of the femoral vein is a method of prophylaxis of pulmonary embolism leaving much to be desired. It may not stop the process from extending, it may require bilateral ligation, and it has no place in therapy other than that involving the legs. In addition to its inadequacies, it carries a morbidity in the

* Received for publication May 7, 1946.

† Lieutenant Colonel, Medical Corps, Army of the United States, formerly Chief of Cardiovascular Section, McCloskey General Hospital, where this work was done.

form of edema which in a series of 202 cases was immediate in 47.5 per cent and late in 42 per cent.

Early in the war it was realized that the morbidity and mortality from thrombophlebitis and pulmonary embolism would be high at a surgical center treating patients with major trauma from high velocity projectiles and crush injuries. Preliminary reports on dicoumarol¹⁰ by the Mayo Clinic group,⁸ Wright,⁹ Bingham,¹⁰ and others offered a possible solution. With their experiences as a guide, this therapy was adopted for use in all cases of embolism, thrombosis and phlebitis.

Dicoumarol acts as an anticoagulant by inducing hypoprothrombinemia, probably through inhibiting the formation of prothrombin in the liver. It may, to some degree, prolong the coagulation time of the blood, but this factor is variable and cannot be used as a means of judging the drug's action. At therapeutic prothrombin levels clotting does not occur, and the vessels of the entire body are protected from thrombosis.^{11, 12} Although clots that are already present probably cannot be affected, they cannot extend and propagate. Since emboli arise from new fresh thrombi only, their development is prevented. The great criticism leveled at dicoumarol is the delay in its effect,¹³ for after the initial dosage there is a lag period of 24 to 72 hours in the development of hypoprothrombinemia during which the patient is not protected from thrombosis. Statistical evidence shows that for some unknown reason, this theoretically justified criticism is not a factual threat. In the present series and in those of other investigators, it was found that no emboli occurred subsequent to institution of therapy. Barker et al.¹⁴ state "In dealing with patients who have had thrombophlebitis or a small pulmonary embolism we have rarely used heparin in addition to dicoumarol and have almost never encountered a second episode of thrombosis or embolism during the one to three days which elapsed between the beginning of administration of dicoumarol and the development of adequate prothrombin deficiency." However, there have been isolated cases reported where thrombosis occurred even during adequate hypoprothrombinemia. In the present study, one case developed thrombophlebitis in a small segment of a superficial vein in the midst of a three week period when the prothrombin level was steadily between 20 and 30 per cent, while the other 59 cases, including 13 with initial symptoms of pulmonary embolism, showed no signs of further vascular involvement. Dicoumarol in dosages that maintain a therapeutic blood prothrombin level is therefore an effective drug in preventing thrombosis. It follows that it is indicated as a prophylactic measure in post-operative patients with a history of phlebitis or embolism where the incidence of recurrence was 43.8 per cent and of subsequent fatal pulmonary embolism 18.3 per cent in cases not receiving dicoumarol.¹⁵

The prerequisite for dicoumarol therapy is the establishment of a test for blood prothrombin time which is accurate and dependable. The most reliable method is Quick's¹⁶ or one of its modifications. The one first used in this study was the Russel viper venom modification.¹⁷ Later, because of the

scarcity of this agent, tissue extract thromboplastin was used. By both methods the normal and the 10 per cent dilution of normal were timed for use as controls against the patient's unknown level. Both methods proved satisfactory. The viper venom method was more easily carried out because its control time is subject to very little variation even over long periods of time, whereas thromboplastin varies continuously and each batch must be tested daily. In order to develop standard technic and determine any factors that might alter the results, approximately 100 tests were carried out. It was interesting to find that determinations after breakfast were considerably higher in per cent prothrombin than those on fasting specimens. Prolonged application of the tourniquet or excessive trauma incident to prolonged attempts at venipuncture also raised the percentage reading toward normal. Only slight variations due to the personal factor were found among the technicians.

The exact therapeutic blood prothrombin level has still to be exactly determined. Some authors advise doubling the control time,⁴ others desire levels of 10 per cent to 30 per cent of normal,¹⁸ while the majority have found 20 per cent to 60 per cent levels to be both effective in preventing thrombosis and safe from the danger of hemorrhage. To accomplish this, fairly large initial doses of dicoumarol must be given, and to hold this lowered percentage, maintenance doses must be administered. It may be compared to digitalis therapy, for one "dicoumarolizes" the patient and then prescribes a daily maintenance dosage. The drug is prepared in the form of 50 or 100 mg. tablets or capsules and is for oral use only. Administration is begun only after a prothrombin test has been carried out and found to be in the region of normal.¹⁹

The initial dose used to induce hypoprothrombinemia has varied among those investigating its action, but most have used a schedule of a single dose of 300 mg. the first day, and 200 mg. the second day,^{20, 21, 22, 14} as was done in this study. It must be emphasized again at this time, that prior to these initial doses and all maintenance doses the plasma prothrombin level must be determined for that day. The single time this rule was disregarded was in a case of extensive thrombophlebitis of the deep veins of the leg and thigh. It was late in the day and rather than delay treatment for determination of the initial prothrombin level, 300 mg. of dicoumarol were prescribed. The next morning, the prothrombin percentage was 16, and it stayed near that level for 22 days. Excessive hypoprothrombinemia and hemorrhage are always potential dangers when the drug is "blindly" prescribed. From 24 to 72 hours are required to attain a therapeutic level of hypoprothrombinemia. After the second day, if the prothrombin time has not dropped satisfactorily, the 200 mg. dose of dicoumarol may be repeated daily until it does start to lower. At that point the dosage must be reduced in the manner later to be described. The lag period in reaching therapeutic prothrombin levels varies in each patient.²² In this series it was once felt that because most of these patients were large men, large initial dosages might drop the prothrombin percentage

more rapidly. This was not entirely true, for doses as high as 600 mg. on two consecutive days required an average of 54 hours to reach a therapeutic level, while the 300 mg. and 200 mg. on consecutive days, a much safer dosage, required only six more hours.

In order properly to administer dicoumarol, the dosages and responses must be graphically recorded. The control times of normal and 10 per cent

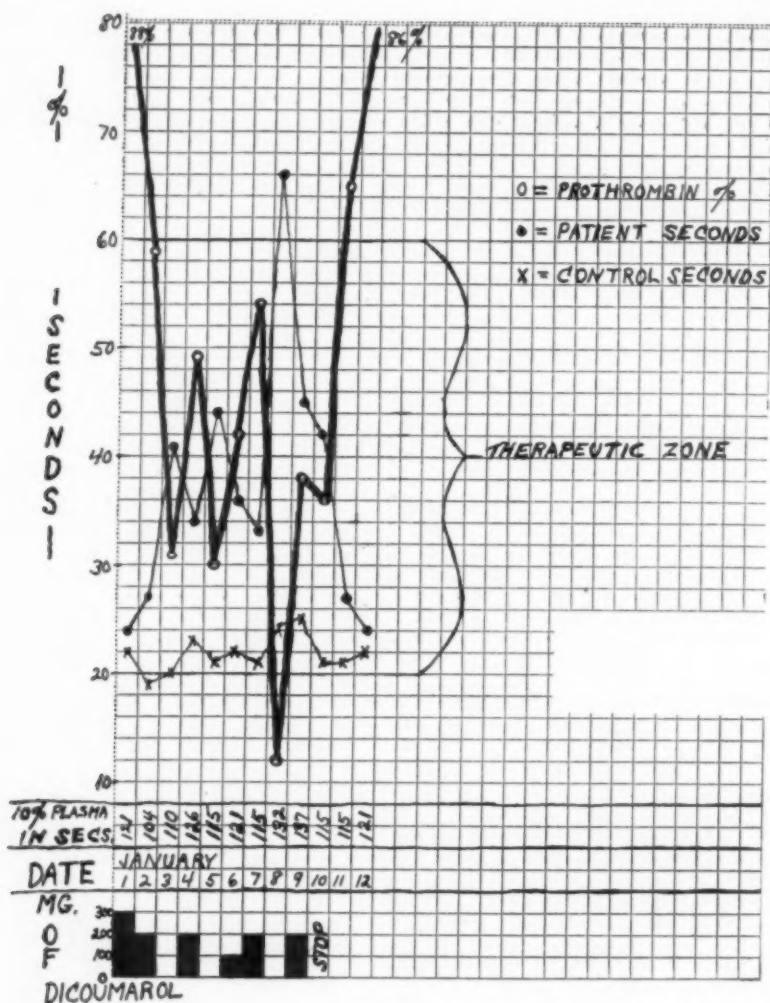


FIG. 1.

dilution of plasma, the patient's time, the patient's percentage prothrombin, and the dosages should be plotted daily as illustrated in figure 1. By thus recording these data, gross laboratory errors are evident, the response of the patient to each day's dosage is seen, and the trend of the curve with relation to the lag period and delay in effect of each dose is visualized.

The maintenance dosage for each day can be estimated from the responses and trend of the curves as plotted. If the percentage is in the upper part of the therapeutic zone, between 40 per cent and 60 per cent, and the curve is rising rapidly, a relatively heavy dose such as 200 mg. of dicoumarol is given. If it is rising rapidly in the lower zone, 20 per cent to 40 per cent, a smaller dosage, possibly 100 mg. would be prescribed. If the curve is almost horizontal in the lower therapeutic levels, 50 mg. or possibly none at all will be administered that day. In this series, the average daily dose of dicoumarol was 129.2 mg., but average dosage cannot be used as an index of treatment.²³ One must follow the graph and anticipate the effect today's dose is going to have on tomorrow's percentage. Only by following this trend and also the response of the patient to previous dosages, can the proper amount of dicoumarol be estimated for that day. In addition, deviations from the expected prothrombin times become conspicuous and allow one to recheck the laboratory and review the patient's status.

Upon discontinuing the administration of dicoumarol, there is a period of continued activity until the effect of the drug has worn off.^{22, 14} During this time, the prothrombin percentage gradually returns to normal. The average time for this to occur is 6.9 days, the shortest being one day and the longest 24 days.

The length of dicoumarol treatment varies with each case. Hypoprothrombinemia is induced as rapidly as possible. When it has been attained, further clotting ceases, and appropriate daily doses continue this inability to thrombose. With no new thromboses possible, the subsequent four or five days are sufficient time to allow all previously formed clots to become safely attached to the vessel wall. When this time has elapsed, the patient is started on gradually increasing exercise, if his primary condition permits. After several days of activity, the chances of thrombosis are remote, so the dicoumarol is stopped and the prothrombin level is allowed to rise.²⁴ In those cases in which the primary illness does not allow resumption of physical activity, the length of therapy must be judged accordingly. For example, one case in this series was a young soldier who developed bilateral ilio-femoral phlebitis that spread up the inferior epigastric veins as high as the costal margins. This came on while the patient had a paraplegia from a contusion of the spinal cord at D. 10. On dicoumarol the propagation ceased and all signs of phlebitis disappeared. It was felt that relatively soon he might regain muscular activity, for he could already move one toe. Dicoumarol was continued for two months, at which time he had fair motion of his toes, feet, and legs. The drug was then stopped, and he made a gradual uncomplicated recovery. In contrast to this case, another patient with paraplegia had a phlebitis of the deep veins of the calf and femoral vein of the right leg. He was placed on dicoumarol for only a two weeks period, for he was permanently paralyzed and the prophylactic use of dicoumarol would have meant lifetime administration, since he would never reach a stage where physical activity would normally prevent thrombosis. The average

number of days of hypoprothrombinemia was 15.5, the longest being 53 days, and the shortest four days. Patients have been reported as having had dicoumarol therapy for as long as three months.¹⁴ The average total dosage was 2004 mg., the largest was 6400 mg., and the smallest 800 mg. Liver and renal function tests, blood counts, and blood chemistry tests remained normal in all the cases investigated in this and other series.^{8, 10} The erythrocyte sedimentation rate tended to be elevated and the coagulation time prolonged.

Hemorrhage is the only toxic effect of dicoumarol. Excessive and uncontrolled dosage has led to fatalities.²⁵ In controlled therapy, hyper-reactors to the drug are encountered rather commonly. As high as 27 per cent of patients have been reported as hyper-reactors, but in this series only nine of the 60 patients (16.6 per cent) showed excessive response to ordinary dosage of dicoumarol. In four of these there was gross hematuria, in two, microscopic hematuria, and in three, no hemorrhagic phenomena at all. No other type of extravasation was observed, although others have reported purpura, oozing from wounds, ulcers, brain injuries or emboli, operative sites, and the gastrointestinal tract during excessive hypoprothrombinemia.^{8, 11, 12, 26} For this reason, daily physical examination and urinalysis are necessary for early detection of the hemorrhagic tendency.

Treatment of hemorrhage and excessively low prothrombin percentages involves restoration of the blood's ability to clot by replacing its deficient prothrombin. On this premise, transfusion of fresh whole blood was first used as the treatment, and was found effective. Since the amount of prothrombin transferred to the patient is proportional to the amount of blood given, several 400 c.c. transfusions may be needed to furnish enough prothrombin to overcome the deficiency. One or two transfusions are usually sufficient greatly to reduce the hemorrhage or cause it to cease completely. These may be repeated every few hours. Stored blood loses its prothrombin, and thus its beneficial action. This physiochemical action has been a useful factor in dicoumarol therapy when blood transfusion is required for the primary illness. Here the fresh blood of the donor would counteract the drug's action through its prothrombin content, but if the donor's blood is stored 24 hours, this action is minimized and tends not to disturb the prothrombin curve of the patient appreciably.

Another method of combating hemorrhage is the use of vitamin K (menadione bisulfite, hykinone), an essential substance for the formation of prothrombin.^{26, 27, 14} It is convenient and immediately available for use, being prepared in relatively inexpensive 10 c.c. ampules containing 60 mg. of the vitamin. This constitutes one therapeutic dose, and is massive when compared to the previously standard dose of 3.2 mg. which was ineffective and earlier had caused this drug to be considered useless in treating hypoprothrombinemia.^{26, 27, 28, 9, 18} It is given slowly intravenously and has shown no side reactions. It is used to have the body rapidly restore its blood prothrombin toward the normal level. This is not immediate, but

shows rise in two hours with maximum effect in eight hours.²⁰ When the quicker action of fresh blood is not urgently needed, this preparation may be used, especially in excessive hypoprothrombinemia without hemorrhage, or where hemorrhage is mild. It may be used also to fortify the action of blood transfusion. In this series, it was used at 12 hour intervals and was repeated twice if necessary. If more active treatment is needed, blood transfusion should be carried out as it was in one of these cases where, in spite of hykinone administration, hematuria persisted, and responded only to fresh blood. In all the other cases of hematuria, bleeding ceased or gradually subsided several hours after vitamin K therapy. In a case of hypoprothrombinemia without hemorrhage, hykinone and blood transfusion had little immediate effect, and it was not until six days later that the prothrombin spontaneously began to rise slowly. None of the cases of hematuria was serious or alarming, and all responded to therapy.

The contraindications for use of dicoumarol therapy are absolute and relative.²² The former are renal insufficiency, hepatic damage, bacterial endocarditis, purpura, bleeding tendencies, recent brain or cord injury. Relative contraindications are ulcers, open wounds, faulty absorption of vitamin K as in gastric, biliary, or bowel damage, and emaciation or severe nutritional deficiency.^{14, 29} The basis for these contraindications are obviously related to disturbance in prothrombin formation or the tendency for hemorrhage.

In 13 of the 56 cases of thrombophlebitis or phlebothrombosis, pulmonary embolism was the initial symptom. All were treated with dicoumarol and all recovered. Statistically, there should have been a 20 per cent mortality, had dicoumarol not been used.^{15, 22} These occurred during the most active days of combat, when 10,742 surgical procedures were carried out, while during the previous year, when dicoumarol was not used, there were four deaths from pulmonary embolism in a series of 2,604 surgical operations.

The thrombosis or phlebitis in these 56 cases ceased propagating in all but one in which for a few days a mild phlebitis in a few centimeters of superficial vein developed during very adequate therapy. In another four cases undergoing operation, which had recent severe phlebitis, dicoumarol was used prophylactically because of the high incidence of recurrence with subsequent operation. The drug was started the first or second day after operation in the usual manner, and effective prothrombin levels were reached the third or fourth postoperative day. No difficulties or complications were encountered, since care was taken to avoid hypoprothrombinemia too early postoperatively. None developed phlebitis or thrombosis. In a case on active therapy (prothrombin 30 per cent), suddenly requiring a major operation, 500 c.c. of blood were immediately given and repeated in four hours. At the time of operation, one hour later, the prothrombin percentage was 60 per cent. Bleeding was not excessive, and the postoperative course was uneventful.

The cases of phlebothrombosis and thrombophlebitis did exceptionally

well. Pain and edema seemed to be much milder on dicoumarol therapy,^{21, 19} and sympathetic blocks were done much less frequently than previously. The degree of chronic edema and residual symptoms also decreased considerably. The patients experienced no subjective discomfort or reaction, they all were comfortable and completely coöperative, and in a much healthier state of mind than those managed previously by surgical ligation of the veins, sympathetic blocks, and prolonged intravenous administration of heparin.

CONCLUSION

1. Dicoumarol is an effective anticoagulant.
2. The initial dosage of 300 mg. the first day, and 200 mg. the second day is the most suitable schedule for inducing hypoprothrombinemia.
3. Maintenance dosage is variable even in the same individual, and the daily plasma prothrombin time is the only index of the drug's action.
4. Hemorrhage is the only toxic action of dicoumarol. It can be controlled by fresh blood or vitamin K.
5. Absolute contraindications for use of dicoumarol are renal insufficiency, hepatic damage, bacterial endocarditis, purpura, bleeding tendencies, and recent brain or cord injury. Relative contraindications are ulcers, open wounds, faulty absorption of vitamin K as found in gastric, biliary, or bowel damage, and emaciation.

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PENICILLIN AND SULFADIAZINE, COMPARED WITH SULFADIAZINE ALONE, IN THE TREATMENT OF PNEUMOCOCCIC PNEUMONIA *

By HARRY F. DOWLING, M.D., F.A.C.P., HUGH H. HUSSEY, M.D.,
F.A.C.P., HAROLD L. HIRSH, M.D., and FRIEDA WILHELM, M.D.,
Washington, D. C.

UNTIL the discovery of penicillin, sulfadiazine and several of its analogues were recognized universally as the drugs of choice in the treatment of pneumococcal pneumonia. When penicillin was shown to be active against pneumococci in vitro, the question of its relationship to the sulfonamides in the treatment of pneumococcal pneumonia became important. At first, since only small quantities of penicillin were available, this drug was reserved for patients who did not make the expected response to sulfonamides, but as the supply increased the problem of whether to treat all patients with penicillin from the start became paramount. In an attempt to solve this problem we decided to treat parallel groups of patients having typed pneumococcal pneumonia with sulfadiazine alone or with sulfadiazine plus penicillin.

PLAN OF THE STUDY

As soon as a patient was admitted to the medical wards of the Gallinger Municipal Hospital with the diagnosis of pneumonia, he was placed either in the group scheduled to receive 6 grams of sulfadiazine immediately, followed by 1 gram every four hours, or in the group which was to receive the same dose of sulfadiazine and penicillin in addition. Patients were assigned to one of these groups in strict alternation, from which there was no deviation, except that when a patient diagnosed on admission as having pneumonia was later found to have some other condition, such as pulmonary infarction or tuberculosis, his name was removed from the group to which it had been assigned and the name of the next patient admitted with the diagnosis of pneumonia was substituted for it.

In each group sulfadiazine was continued until the temperature had been within normal limits for about three or four days. Patients in the group treated with both sulfadiazine and penicillin received the first dose of each drug at the same time. The first three patients of this group were given 100,000 units of penicillin by continuous intramuscular drip by the method described by two of us¹ over a period of 12 hours. The next 14 patients received 200,000 units by the same route during the course of 24 hours. By this time penicillin had become more freely available, and it was decided to

* Received for publication March 16, 1946.

From the Health Department of the District of Columbia, The Gallinger Municipal Hospital, and the Departments of Medicine, the George Washington and Georgetown Universities.

administer 15,000 units at two-hour intervals for 36 doses, making a total of 540,000 units in 72 hours of treatment. This schedule was adhered to for the remaining 76 patients, unless death intervened before the entire amount was given.

Four patients in the penicillin-sulfadiazine group were given additional penicillin after the termination of the scheduled regime, because they did not appear to be responding satisfactorily, or because of complications. All of these patients recovered. Two patients in the sulfadiazine series did not improve on sulfadiazine treatment and were given penicillin in addition nine and 12 days, respectively, after the sulfadiazine had been started. Both of these patients died.

Sputum for typing and blood for culture were collected on each patient before any treatment was given, and at suitable intervals thereafter. One or more roentgenograms of the chest were taken on each patient. Blood counts were made initially on each patient and frequently (usually every other day) thereafter, as long as the temperature remained elevated or sulfadiazine was being administered.

RESULTS

There were 94 patients with typed pneumococcic pneumonia in each group. Among those treated with sulfadiazine alone, nine patients (9.6 per cent) died, as compared with four (4.3 per cent) who died in the penicillin-sulfadiazine group. Two patients in the sulfadiazine group and one in the penicillin-sulfadiazine group died within 12 hours of the initiation of treatment. The two groups have been compared with respect to certain factors which are generally known to affect the prognosis in pneumonia,

TABLE I
Results of Treatment with Sulfadiazine, or Penicillin plus Sulfadiazine,
Arranged According to Type of Pneumococcus

Type	Sulfadiazine		Penicillin and Sulfadiazine	
	No. of Patients	Died	No. of Patients	Died
1	8	2	13	1
2	3	0	5	0
3	12	3	7	0
4	6	0	6	0
5	2	0	2	0
6	2	0	2	0
7	9	1	12	0
8	6	1	6	0
12	6	0	9	1
13	9	0	4	0
14	7	0	5	0
18	5	0	4	0
Other types	19	2	19	2
Total	94	9 (9.6%)	94	4 (4.3%)

namely, the type of the infecting pneumococcus, the age of the patient, the presence of associated diseases, and the incidence of bacteremia. As shown in table 1, the type distribution of pneumococci was approximately the same for the two groups.

When the ages of the patients in the two groups are compared (table 2) it is seen that there were more patients in the penicillin-sulfadiazine series under the age of 41 than there were in the sulfadiazine group. Nevertheless, there were no deaths in this age-period when the combined treatment was used, while there were three sulfadiazine-treated patients in the same age-period who died. In table 3 are listed the patients who had associated diseases. There were 12 of these in the sulfadiazine group, of whom four died, and 14 in the penicillin-sulfadiazine group, of whom one died.

TABLE II
Results of Treatment with Sulfadiazine, or Penicillin plus Sulfadiazine,
Arranged According to Age of the Patient

Age-Group	Sulfadiazine		Penicillin and Sulfadiazine	
	No. of Patients	Died	No. of Patients	Died
12-20	8	0	15	0
21-30	17	1	24	0
31-40	22	2	27	0
41-50	19	0	27	2
51-60	16	2	5	0
61-70	3	1	3	1
71 and over	9	3	3	1
Total	94	9	94	4

Owing to the present shortage of technical personnel, it was necessary for blood cultures to be transported across the city to the Laboratory of the Health Department of the District of Columbia, where they were incubated and studied. Unfortunately, as a result of this, a great many of them became contaminated or failed to grow bacteria, so that only 11 patients were reported as having positive blood cultures, two in the sulfadiazine group and nine in the penicillin-sulfadiazine group. All of these patients recovered. Judging by our past experience in managing patients with pneumococcal pneumonia in the same hospital, and by the clinical appearance of the patients in the present series, we feel that another method of handling these cultures would have resulted in a much higher incidence of bacteremia.

From table 4, it will be noted that the complications were few and inconsequential in both groups with the exception of one patient in the penicillin-sulfadiazine group who developed empyema. He entered the hospital acutely ill with delirium tremens and pneumonia of an entire lung caused by the Type 33 pneumococcus. His temperature did not fall to normal in spite of treatment with sulfadiazine and penicillin. When the empyema was discovered several aspirations were made and then thoracotomy was done. He

TABLE III
Diseases Associated with the Pneumonia and Their Relation to Mortality

Diseases	Sulfadiazine		Penicillin and Sulfadiazine	
	No. of Patients	Died	No. of Patients	Died
Congestive heart failure	1	1	2	1
Auricular fibrillation	1	0	—	—
Auricular paroxysmal tachycardia	1	1	—	—
Acute alcoholism	3	0	6	0
Chronic bronchitis	2	0	1	0
Cirrhosis of liver	1	0	—	—
Bronchial asthma	1*	0	1	0
Carcinoma of stomach	1*	1	—	—
Pregnancy	—	—	1	0
Chronic glomerulonephritis	—	—	1	0
Subarachnoid hemorrhage	—	—	1	0
Pulmonary tuberculosis	1	1	—	—
Hemiplegia	—	—	1	0
Total	12	4	14	1

* Hypertensive heart disease also present.

TABLE IV
Complications of Pneumococcal Pneumonia in Patients Treated with Sulfadiazine or Penicillin plus Sulfadiazine

Complication	Sulfadiazine		Penicillin plus Sulfadiazine	
	No. of Patients	Died	No. of Patients	Died
Pleural effusion	—	—	3	0
Empyema	—	—	1	1
Delayed resolution	3	0	4	0
Spread into another lobe	1	0	—	—
Otitis media	1	0	1	0

improved for a while, but complete drainage was never established and he died 83 days after admission and 65 days after the thoracotomy. It is quite possible that the empyema was already present when this patient was admitted to the hospital, since he had been ill for eight days at that time and had received no treatment.

We have compared the two groups with respect to the time required for the temperature to fall permanently below 101° F., and found that they were strikingly similar in this respect. Such a drop in the temperature occurred within 24 hours in 47 patients in the sulfadiazine group and in 48 patients in the penicillin-sulfadiazine group.

No toxic effects were observed from the administration of penicillin. One patient developed drug fever, two dermatitis, and one gross hematuria from sulfadiazine. All of the patients received 6 grams of sodium bicarbonate with the initial dose of sulfadiazine and 3 grams with each subsequent dose.

COMMENT

As penicillin becomes more and more available, the physician is faced with the question of whether to treat all patients with pneumonia by the administration of one of the sulfonamides, reserving penicillin for use in case the response is not satisfactory, or to use penicillin, alone or in combination with a sulfonamide, from the very beginning. It seemed important to us to determine first of all whether the employment of penicillin offers any additional benefit over the use of sulfadiazine alone. In comparable groups of alternate patients treated with sulfadiazine alone and sulfadiazine plus penicillin, the lower case-fatality rate observed in the latter group, while not statistically significant, was highly suggestive. The results obtained in the two groups did not differ materially with regard to the rapidity of the fall in temperature or the presence of complications.

Studies such as the present one cannot be expected to do more than suggest the answer to the question as to the best method of treatment of pneumococcic pneumonia. In a series of cases, including those collected from the literature and those treated by one of us,² the death-rate from pneumococcic pneumonia was found to be as follows: among 1,616 patients receiving no specific treatment, 38.0 per cent; among 1,248 patients who were given specific antipneumococcic serum, 17.2 per cent; among 3,777 patients who received sulfonamides (with or without specific antiserum in addition) 13.5 per cent. From the data available at the present time, we have reason to expect the case-fatality rate to be lowered still further with the use of penicillin. Tillett and his associates³ and Bunn and his co-workers⁴ reported rates of 6.3 per cent and 2.2 per cent, respectively. Meads et al.⁵ used penicillin in the treatment of 54 severe cases of pneumococcic pneumonia with 10 deaths. Kinsman and his associates⁶ reported no deaths in a group of 75 soldiers treated with penicillin. The age and physical condition of these patients undoubtedly account for these excellent results, since there were likewise no deaths among 100 soldiers treated with sulfadiazine during the previous year at the same hospital.

Although the foregoing reports do not demonstrate conclusively that penicillin is superior to the sulfonamides in the treatment of pneumococcic pneumonia, nevertheless, when they are taken in conjunction with our results, they do suggest that this is true. By the time the number of patients who have been treated with penicillin approximates the number of those treated with the other effective agents, penicillin may have been found to be the most effective drug. Whether it should be used alone or in conjunction with the sulfonamides is a question which must be settled by further investigation.

In spite of the proper employment of the best therapeutic agents available, some patients with pneumococcic pneumonia will still die. In general, they are the patients in the older age-groups, those with complications, or those in whom treatment is initiated late because of delay in reporting to the phy-

sician or mistaken diagnosis. This is evident in the present group of patients treated with penicillin and sulfadiazine. Of the four patients who died, one was admitted in delirium tremens on the ninth day of the disease and died of empyema which may have been present before treatment was begun or may have developed during the treatment. Two were in the older age-groups, one being 80 years of age and the other 61. The latter also suffered from congestive heart failure and was a chronic alcoholic. The remaining patient was 42 years of age and was admitted in a moribund condition and died six hours after treatment was started. It is to such patients as these that our attention should be directed if we wish to lower the mortality rate still further.

It is worth noting that we did not encounter any instances of relapse or of secondary rise in fever in the patients treated with penicillin and sulfadiazine, even though the administration of penicillin was almost always discontinued 72 hours after treatment was begun. Such relapses have been reported⁸ in pneumonia patients treated for short periods of time with penicillin alone. Our good results were undoubtedly due to the fact that the sulfadiazine therapy was continued in every case until the temperature had been normal for two or more days. This fact might constitute a good argument for giving sulfonamides to patients with pneumonia along with penicillin, at least until penicillin becomes cheap enough so that its administration can be continued through two or more days of normal temperature.

SUMMARY AND CONCLUSIONS

1. Among 94 patients with typed pneumococcic pneumonia treated with a combination of penicillin and sulfadiazine, there were four (4.3 per cent) deaths, as compared with nine (9.6 per cent) deaths among a group of 94 patients treated in alternation with sulfadiazine alone.

2. There was no significant difference in the speed at which the temperature fell or in the development of complications of the pneumonia in the two groups.

3. The present study, taken together with the literature available at the present time, suggests that penicillin, when added to sulfadiazine for the treatment of pneumococcic pneumonia, is more effective than sulfadiazine alone.

The authors wish to thank Dr. George C. Ruhland, Dr. James G. Cumming, and Dr. John E. Noble for their coöperation, and Dr. J. B. Holland and Mrs. Rose Breen for technical assistance.

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TREATMENT OF CARDIOVASCULAR SYPHILIS WITH PENICILLIN *

By HENRY I. RUSSEK, M.D., F.A.C.P., JOHN C. CUTLER, M.D., STEPHEN
A. FROMER, M.D., *Staten Island, New York*, and BURTON L.
ZOHMAN, M.D., F.A.C.P., *Brooklyn, New York*

Most authorities agree that specific therapy in cardiovascular syphilis favorably influences the course of the disease and increases life expectancy.¹ According to Scott² "any medication that tends to allay the process in the aorta and thus prevent its spread to the aortic orifice or retard the development of aneurysm, may add years to the patient's life." Moore and his associates,³ using preparatory heavy metals to avoid the possibility of Herxheimer reaction, followed by conservative arsenotherapy, have reported striking effects on the mortality rate and the average duration of life in this form of the disease.

The demonstration by Mahoney, Arnold and Harris,⁴ and others, that syphilitic lesions undergo rapid involution under penicillin therapy has suggested the use of this drug in the treatment of syphilis of the cardiovascular system. Wile,⁵ however, has warned of the likelihood of untoward reactions which might arise from the use of penicillin in this condition. Dolkart and Schwemlein⁶ have similarly stressed the danger of a therapeutic paradox in their recent report of two cases in which penicillin was thought to have induced untoward effects. In the first of their cases a single injection of 10,000 units of penicillin was administered on each of the first two days of treatment. On the third day, after the injection of 20,000 units of the drug, anginal attacks became more frequent and premature ventricular contractions were noted. In the second case, precordial pain developed after penicillin had been administered in the dosage of 20,000 units every two hours for a period of three days. In both instances the authors discontinued the use of the drug.

The experience of the writers with penicillin in relatively large dosage in 15 consecutive cases of syphilitic aortitis, including four cases of aortic aneurysm does not suggest any appreciable danger from this form of therapy. As shown in the accompanying table the dosage usually employed was 40,000 units every two hours for 85 doses. In one instance, Case 2, mild substernal pain recurred intermittently at rest on the third day of treatment but disappeared after several hours, without interruption of therapy. This patient showed the greatest subsequent improvement from treatment in the present

* Received for publication April 27, 1946.

From the Cardiovascular Research Division and Venereal Disease Research Laboratory of the U. S. Marine Hospital, Staten Island, New York.

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TABLE I

Case	Age	History	Prev. Treatment	Lesion	Serology	Penicillin	Reactions	Remarks
1	48	Negative	None	Syphilitic aortitis	Maz. 4+ Kahn 4+	40,000 u. q. 2 hours— 85 doses	None	Spinal fluid Wassermann 4+
2	45	Chancre in 1925	None until 1944 then 25 inj. of As and Bi	Double aortic aneurysm	Maz. + Kahn-neg.	40,000 u. q. 2 hours— 85 doses	Mild sub-sternal pain on 3rd day of treatment	Marked clinical improvement
3	52	Negative	None	Aortic aneurysm	Maz. 4+ Kahn 4+	40,000 u. q. 2 hours— 85 doses	None	Improved
4	42	Chancre in 1935	16 As and 16 Bi inj. in 1935	Aortic aneurysm	Maz. 1+ Kahn 3+	40,000 u. q. 2 hours— 85 doses	None	
5	40	Chancre in 1930	None until 1943 then 15 As and 2 Bi injections	Syphilitic aortitis	Maz. 4+ Kahn 4+	40,000 u. q. 2 hours— 85 doses	None	Marked clinical improvement
6	59	Negative	None	Syphilitic aortitis	Maz. 4+ Kahn 4+	40,000 u. q. 2 hours— 85 doses	None	
7	45	None	None	Syphilitic aortitis	Maz. 4+ Kahn 4+	40,000 u. q. 2 hours— 85 doses	None	
8	52	Negative	None	Syphilitic aortitis	Maz. 4+ Kahn 4+	60,000 u. q. 2 hours— 85 doses	None	Spinal fluid Wassermann 4+
9	51	Negative	None	Syphilitic aortitis	Maz. 4+ Kahn 4+	20,000 u. q. 2 hours— 85 doses	None	
10	35	Chancre in 1940	Inadequate treat.—1940–1944	Syphilitic aortitis	Maz. 3+ Kahn 2+	40,000 u. q. 2 hours— 85 doses	None	
11	40	Chancre in 1930	None until 1944—then alter. courses As and Bi	Syphilitic aortitis	Maz. 4+ Kahn 4+	40,000 u. q. 3 hours— 125 doses	None	
12	57	Chancre in 1929	Inadequate treat.—1931	Syphilitic aortitis	Maz. 4+ Kahn 4+	40,000 u. q. 2 hours— 85 doses	None	Improved
13	40	None	Inadequate treatment	Aortic aneurysm	Maz. 4+ Kahn 4+	40,000 u. q. 2 hours— 85 doses	None	
14	46	Chancre in 1932	Inadequate treatment in 1940	Syphilitic aortitis	Maz. 3+ Kahn 2+	40,000 u. q. 2 hours— 85 doses	None	
15	48	None	None	Syphilitic aortitis	Maz. 4+ Kahn 4+	40,000 u. q. 2 hours— 85 doses	None	

series. Substernal pain on effort, which was manifested even after a control period of prolonged bed rest, almost completely abated following the course of penicillin. Three other cases similarly appeared to manifest significant increments in coronary reserve after treatment. However, electrocardiographic confirmation of such improvement was not obtained. As was anticipated, no noteworthy change in serologic reactions was observed in the follow-up period, which varied from one to three months.

From these observations it would appear that significant untoward reactions from penicillin are uncommon in cardiovascular syphilis. That this similarly applies to other forms of late and latent syphilis is indicated by the failure to encounter a single instance of therapeutic paradox in 389 cases of central nervous system and latent syphilis treated with penicillin on the Venereal Disease Service of the U. S. Marine Hospital in Staten Island. These findings are in striking contrast with the frequency of Herxheimer reactions noted in similarly treated cases of early syphilis in which the incidence approximated 90 per cent. It is possible, moreover, that such reactions as do occur in patients suffering from cardiovascular syphilis may not necessarily warrant discontinuance of therapy. Further observations may indicate that the success of this form of treatment justifies the risk entailed.

SUMMARY AND CONCLUSIONS

Fifteen consecutive cases of cardiovascular syphilis, including four with aortic aneurysm, were treated with penicillin in the dosage of 40,000 units every two hours for 85 doses. No significant untoward reactions necessitating discontinuance of the drug were encountered. Four patients showed distinct improvement in coronary reserve following treatment. It is concluded that harmful reactions to penicillin are uncommon in cardiovascular syphilis during the treatment and early post-treatment periods and that this form of therapy warrants further evaluation.

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CASE REPORTS

GENERALIZED XANTHOMATOSIS WITH PULMONARY, SKELETAL AND CEREBRAL MANIFESTATIONS: REPORT OF A CASE*

By EULYSS R. TROXLER, M.D., *Roanoke, Virginia* and DAVID NIEMETZ, M.D.,
Los Angeles, California

IN recent literature there have appeared numerous case reports of lipoid granulomatosis or xanthomatosis with its varied clinical manifestations. Typical Hand-Schüller-Christian disease with its triad of symptoms, consisting of defects in membranous bones, exophthalmos and diabetes insipidus, is now considered as the craniohypophyseal localization of lipoid granulomatosis.¹ On the basis of pathological studies, Green and Farber² have concluded that eosinophilic or solitary granuloma of bone is one form of generalized xanthomatosis and not a new disease entity. These authors also describe Letterer-Siwe disease or reticulo-endotheliosis as the same pathological process seen in Hand-Schüller-Christian disease. Wherever there is reticulo-endothelium there can be lipoid granulomatosis. Thus, the clinical symptoms produced depend upon the tissues involved and the degree of involvement. The following case is one with pulmonary, skeletal and cerebral involvement.

CASE REPORT

P. V. G., a white man, aged 35, was admitted to the Los Angeles County General Hospital on November 27, 1942 with the complaint of increasing shortness of breath of three days' duration.

The past medical, familial and marital histories were irrelevant. The patient stated that at the age of 20 years many of his teeth became loose and began to fall out. A diagnosis of "trench mouth" was made, following which all of his remaining teeth were removed. In 1933 he awoke one morning extremely thirsty, requiring large amounts of water, which failed to satisfy him. Frequency of urination and excessive amounts of urine were noted simultaneously. At this same time he had pains in the left lumbar region and the upper right thigh. The pains were intermittent and resulted in weakness of the right leg. There had been no previous history of trauma. In July 1934 he experienced a sharp pain in the left chest after throwing a rock. This pain became more severe and was accompanied by shortness of breath. With these symptoms he was seen in the Oklahoma University Hospital out-patient clinic, where a roentgen-ray diagnosis of left pneumothorax and pulmonary tuberculosis was made. He was admitted to a sanatorium, where, after two weeks, his symptoms disappeared and he was told that he did not have tuberculosis.

In October 1934 he entered the Oklahoma University Hospital because of excessive thirst and urination, which had continued since 1933. Aquamedrin, intermedrin and obstetrical pituitrin caused a moderate reduction in intake and output of

* Received for publication July 17, 1945.

From the University of Southern California Medical School and the Los Angeles County General Hospital; aided by the Michael J. Connell Charities, Ltd.

fluid. Roentgenograms revealed normal skull series and generalized fibrosis of lungs. The impression at that time was old fibrous tuberculosis, although multiple small cysts were not ruled out. He was discharged after one month, only to be readmitted three weeks later, complaining of pain in his left chest and shortness of breath, which appeared after a paroxysm of coughing, induced by "flu". Almost complete collapse of the left lung was found. No specific therapy was given for the pulmonary lesions, but the previous treatment for diabetes insipidus was successfully resumed.

In 1938 he made an uneventful recovery from an automobile accident resulting in fractured right ribs and lacerations of the head.

In June 1939 he was again admitted to the Oklahoma University Hospital complaining of pain in his back and legs, excess thirst and frequency of urination. Roent-

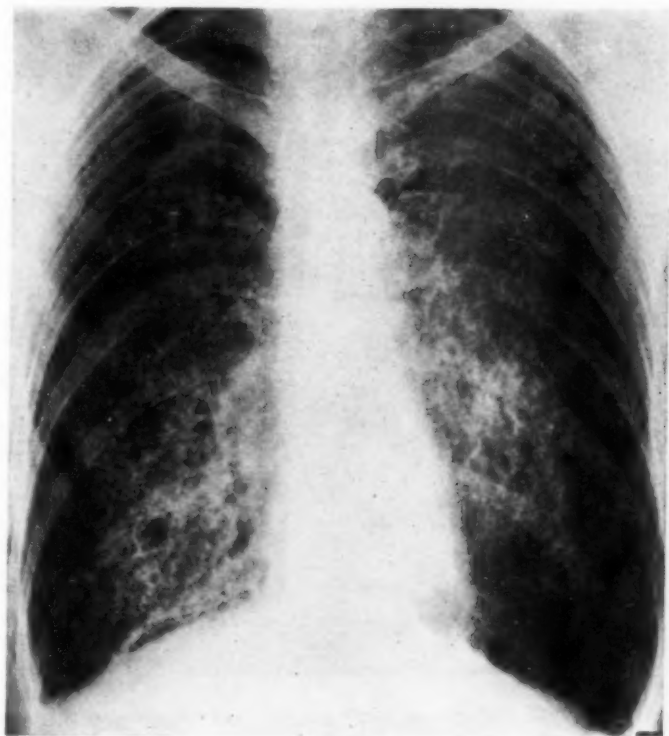


FIG. 1. November 27, 1942. Bilateral pneumothorax and marked fibrosis of lungs.

genograms revealed large cystic areas with well defined borders involving both iliac bones, the right ischium and pubic bone and the neck and trochanteric areas of both femora. An area of destruction involving the anterior portion of the body of the first lumbar vertebra was also noted. A diagnosis of osteitis fibrosa cystica was made. Again he was put on obstetrical pituitrin daily, with marked response. He was discharged in two weeks, being advised to inject $\frac{1}{2}$ c.c. of pituitrin daily.

His final admission to the Oklahoma University Hospital was in May 1940 with similar complaints of thirst and excessive urination. He had been unable to afford pituitrin. He also complained of marked weakness of his legs and was forced to use crutches for walking. Marked muscular atrophy was observed, being more marked in the lower extremities. Slight flexion contractures of the thighs and knees were

present. A slight left scoliosis in the lower dorsal area with abnormal prominence and tenderness of the twelfth dorsal vertebra was noted. Upper extremity reflexes were hyperactive. Fluid intake and output averaged five to six liters per 24 hours at this time. Roentgenograms were found the same as in 1939 except for a healed pathological fracture of the right femur.

The patient was admitted to the Los Angeles County General Hospital November 27, 1942. Seven days previously he had developed a cough which he attributed to excessive smoking. He had noticed pain in the left chest when he tried to lie on his left side. Three days later the right side of his chest had become painful also. This was followed by sudden onset of shortness of breath. Owing to progression of symptoms, he came to the hospital.



FIG. 2. January 12, 1943. Numerous large and small cystic areas in pelvis and femora.

Physical examination revealed a poorly developed and poorly nourished male who appeared older than his age. He was in severe respiratory distress, and his lips and nail beds were moderately cyanotic. Temperature was normal and pulse rate was 125. Respirations were 38 and blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. The mouth was edentulous. The chest revealed no lag and equal expansion bilaterally. Tactile fremitus was markedly diminished bilaterally. The lungs were hyperresonant. Breath and voice sounds were markedly diminished except in a small area between the scapulae. Cardiac dullness was absent and the heart sounds were faint. Slight left dorsolumbar scoliosis and kyphosis were noted. Generalized weakness and atrophy were present in the lower extremities. The patient could not walk without the aid of crutches.

Roentgenograms of the chest revealed the right lung to be approximately 60 per cent expanded and the left lung approximately 70 per cent (figure 1). On the

right, there were several adhesions in the second interspace anteriorly, and on the left the pleura was bound down by adhesions in the entire apical and subapical areas. Both leaves of the diaphragm were flattened and markedly depressed. The parenchymal tissue of both lungs showed marked accentuation of the reticular pattern with several emphysematous blebs.

Because of the severe dyspnea, oxygen inhalations were started immediately. This was followed by numerous aspirations of air from both pleural cavities over a period of 12 days. Finally a water trap suction was used for half a day with marked symptomatic improvement. The patient was discharged after one month, having been asymptomatic for about two weeks. Roentgenograms taken upon discharge



FIG. 3. February 6, 1943. Photomicrograph of a section from a lesion in the right ilium. Numerous eosinophiles and large macrophages with foamy cytoplasm are seen. (Hematoxylin and eosin stain. Magnification 250 diameters.)

showed the left lung completely expanded and the right lung approximately 70 per cent expanded.

The patient was seen in the out-patient department January 11, 1943, still using crutches to walk. He complained of respiratory difficulty, though a roentgenogram revealed the right lung to be approximately 50 per cent expanded. Roentgenograms of the pelvis and femora revealed large cystic areas in both iliac crests and above the acetabula (figure 2). The borders of these cystic areas were sclerotic in most instances. Similar cystic areas were present in the trochanteric and subtrochanteric areas of the femora. There was moderate atrophy of the shafts of the femora, consistent with disuse. The lumbar spine revealed a wedging and narrowing of the first lumbar vertebra with a large destructive lesion in the ventral portion of the body.

There was a left-sided scoliosis, with the apex between the first and second lumbar vertebrae.

The patient was readmitted to the Los Angeles County General Hospital on February 1, 1943 for more complete examination and study. At that time there were no complaints except for an occasional dull aching pain in the right thigh. He was drinking two gallons of water daily, which was not as much as in the past. His physical examination was essentially the same as on the previous admission except for absence of pneumothorax.

Laboratory findings revealed water-clear urine with a specific gravity of 1.002. No albumin or sugar was found and the microscopic examination was essentially

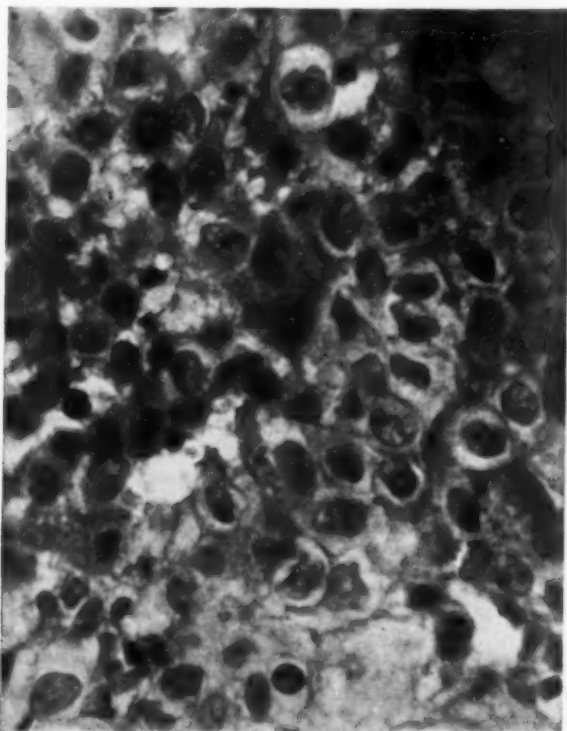


FIG. 4. February 6, 1943. Photomicrograph from the same section showing characteristic foamy cells with sharp cell borders. (Hematoxylin and eosin stain. Magnification 500 diameters.)

negative. The urinary output varied between 6 to 10 liters per 24 hours. The Mosenthal test revealed urinary concentration to a specific gravity of 1.005 in nine hours with a loss of seven pounds in weight. Four liters of urine were excreted. At this time the patient became very uncomfortable and demanded fluids. Hemoglobin, blood count and differential were normal.

Numerous blood chemistry determinations were done at the Oklahoma University Hospital beginning in 1934 and continuing through 1940, all of which were within normal limits except for the glucose tolerance tests. Similar results have been reported in the Los Angeles County General Hospital. The concentrations of various substances tested for in milligrams per 100 cubic centimeters of serum are as follows, with these figures representing averages of several tests and the number of tests

appearing in parentheses: Calcium (5) 9.6; phosphorus (3) 3.6; uric acid (1) 3.5; cholesterol (4) 195; cholesterol esters (4) 67.3. A single non-protein nitrogen determination revealed 35 milligrams per 100 cubic centimeters of whole blood. The average of three alkaline phosphatase determinations was 3.76 Bodansky units, while a single acid phosphatase determination revealed 2.1 Bodansky units. The serum albumin was 4.7 grams and the serum globulin 2.6 grams per 100 cubic centimeters of serum. The five-hour oral glucose tolerance tests revealed the following results: 82.9, 99.5, 63.3, 68.5, 73.5 mg.; 80, 133, 121, 46, 59, 76 mg.; 84, 148, 125, 98, 84 mg. per 100 cubic centimeters of whole blood. Repeated Wassermann and Kahn tests were negative. A 24 hour excretion of 6 liters of urine contained 528 mg. of calcium,

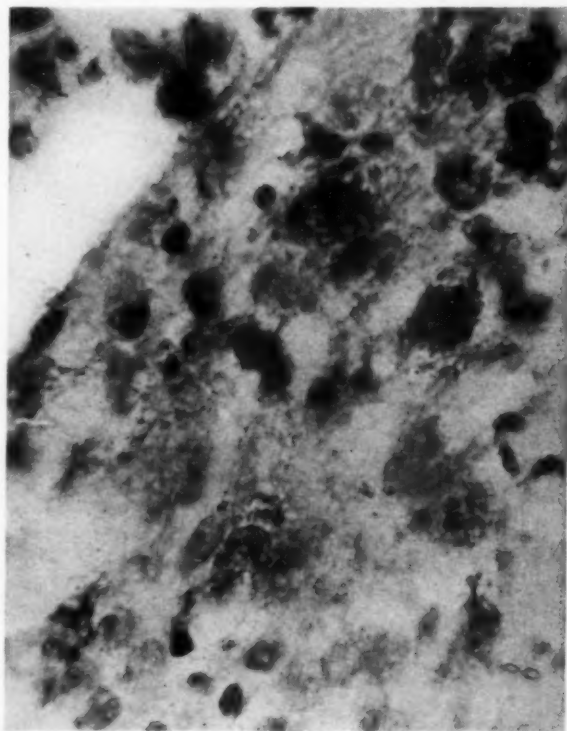


FIG. 5. February 6, 1943. Photomicrograph from the same section reveals fat droplets throughout the foam cells. (Osmic acid stain. Magnification 500 diameters.)

On February 6, 1943 a biopsy was taken from the right ilium under a general anesthetic. Grossly, the cystic area explored was filled with grayish-yellow, fibrous tissue. The bone bordering the cyst was more dense than the surrounding bone. There was no abnormal bleeding about this particular cystic area. Microscopic examination revealed a granulomatous process with reticulum-type cells present in both large and small groups. Many of these cells were foamy in appearance with rather sharp cell borders. Large numbers of eosinophiles were seen scattered throughout. Fat stain (osmic acid) revealed many fat droplets within the foam cells (figures 3, 4 and 5). Smears and cultures of the specimen removed at biopsy revealed no aerobic or anaerobic bacteria.

Following operation, the patient was started on 1 c.c. of surgical pituitrin, following which there was slight gain in weight but very little improvement of his urinary

output. Two weeks later posterior pituitary powder was given in 2 grain doses three times a day by nasal insufflation. For the first time in 10 years his fluid intake and output decreased markedly, approaching normal quantities. On the same day pituitary powder was begun, he was started on a course of roentgen-ray therapy over the pelvic bones. Through each of five portals the patient received, in divided doses, 400 roentgen units in air. The technical factors were 200 KV, 20 MA, Cu 0.5, Al 2.0, T.S.D. 50 cm., (H. V. L. 1.0 Cu).

After about one month's stay in the hospital the patient was discharged to the outpatient department. He improved symptomatically and was able to walk without the aid of crutches.



FIG. 6. May 17, 1943. Pathological fracture through cystic areas of right femur after five weeks in traction. Abundant callus present.

On April 12, 1943 he fell, incurring pain in the right thigh and hip. Reentry into the hospital at that time revealed characteristic signs and symptoms of a subtrochanteric fracture of the right hip. Roentgenograms revealed a pathological fracture through cystic areas in the subtrochanteric region. Russell traction was applied immediately after admission. After two months in traction, roentgenograms revealed good position of the fracture and adequate callus (figure 6). Traction was removed and the patient was discharged.

Repeated roentgenograms taken during the following year and a half showed no significant change in the bony lesions about the spine and pelvis. Films of the chest revealed almost complete disappearance of the pneumothorax except for a small area

in the right costophrenic sulcus (figure 7). During this interval the patient was able to control his diabetes insipidus with pituitary powder. There had been one episode of coughing with slight hemoptysis and chest pain but without evidence of pneumothorax on physical examination. Except for occasional slight pain in the right hip, he had had no symptoms referable to his healed fracture.

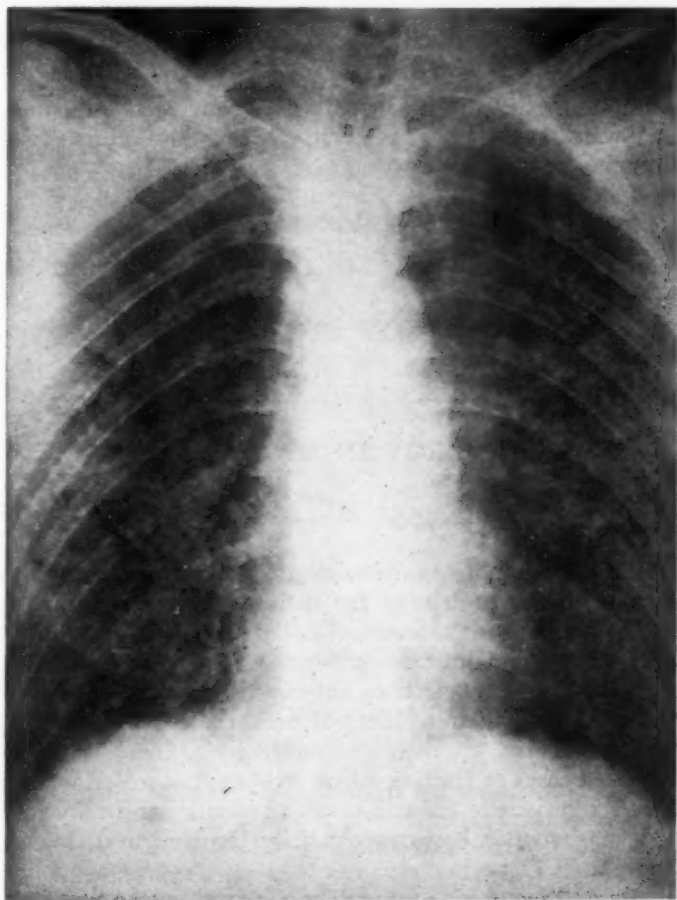


FIG. 7. May 28, 1943. Nearly complete disappearance of pneumothorax. Extensive fibrosis is present.

COMMENT

The case reported illustrates some of the protean manifestations which may occur in generalized xanthomatosis. The definitive diagnosis was made by biopsy of a bone lesion. There was extreme pulmonary involvement with fibrosis and resulting bilateral pneumothorax. It was this condition which forced the patient to seek hospital care. After pleural aspirations the lungs remained expanded for a year and a half without further treatment. Because of advanced fibrosis within the lungs, roentgen therapy to these areas was deemed inadvisable.

Apparent hypophyseal involvement produced diabetes insipidus which was well controlled by the use of posterior pituitary powder.

Bone lesions were limited to vertebrae, pelvis and upper portions of the femora. The pelvic lesions did not alter in size following roentgen therapy. A pathological fracture occurred through the lesions in the right femur. This healed with conservative treatment and without unusual delay.

SUMMARY

A case of generalized xanthomatosis with involvement of bone, lungs and cerebrum has been presented. The unusual complication of bilateral spontaneous pneumothorax occurred in this case.

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ALLERGY IN MALARIA *

By HARVEY F. GRAZIER, Captain, MC, AUS, *Johnstown, Pennsylvania*

THE various manifestations of malarial infection are common knowledge, but specific sensitivity to the protein of the malarial parasite is almost a medical curiosity. References to such a condition in the available literature are very few, and detailed case reports almost non-existent. The relationship between urticaria and malarial infection has been infrequently observed over the past 25 years, but as late as 1939 the possibility of urticaria existing coincidentally with and not related to malarial infection was under discussion. In 1928 Thonnard-Neumann described cases in Haiti in which treatment of malaria cured coexistent asthma. More recently urticaria as a result of specific sensitivity to the malarial parasite has been shown in cases reported by Gouriou in 1938, Chatterjee in 1939, Sen Gupta in 1942, and others.

The case reported below was intimately observed by the writer, resulting, in contrast to previous reports of this condition, in considerable available detail.

CASE REPORT

A 26-year old white male in excellent health entered the Solomon Island area in the summer of 1943. He immediately began to take suppressive atabrine. On August 27, 1943 the patient developed generalized urticaria manifested by small wheals over the entire body. This persisted about two hours and disappeared without treatment. Suppressives atabrine was continued. On September 30, 1943 the patient developed angioneurotic edema of both lips with concomitant swelling of the forehead and eyelids and again the generalized urticaria previously noted. This episode occurred about mid-day and was controlled with adrenalin 1:1000 in 0.5 c.c. doses at hourly intervals.

* Received for publication August 10, 1945.

Because he felt slight chilliness, his temperature was taken, found to be 102° F. and was thought to be due to the adrenalin. The following day the patient felt perfectly well, and no sign of allergy was noted. About mid-day October 2, 1943, 48 hours after the initial attack, the patient again developed angioneurotic edema and generalized urticaria as described above. The attack was controlled in similar manner, and again the chilliness and fever of 102.2° F. were noted. In the late afternoon the patient complained of severe frontal headache, mild backache and general malaise. A clinical diagnosis of malaria was made and routine atabrine therapy instituted. Thick and thin blood smears taken on the mornings of October 3 and October 4 (after 9 grains of atabrine) were negative for malarial parasites. The course of atabrine was completed within seven days, and no recurrence of allergic manifestations or signs and symptoms of malaria occurred. Suppressives atabrine was continued. The patient was in excellent health until November 11, 1943 when about mid-day of that date without warning he developed angioneurotic edema with swelling of the forehead, eyelids, lips and generalized urticaria. This was controlled with adrenalin 1:1000 given in 0.5 c.c. subcutaneous injections at half-hourly intervals and then at hourly intervals over a period of four hours for a total dosage of 3 c.c. Because of previous experiences and not because of any chilliness or malaise the temperature was taken and found to be 101.2° F. The following day the patient felt well and nothing unusual occurred. On November 13, 1943 there was an exact duplication of the allergic manifestations which had occurred 48 hours previously, and this was controlled in similar manner though more adrenalin was necessary. However, following subsidence of the urticaria the patient had a slight headache and slight malaise. Temperature at this time was 102.2° F. On November 14, 1943 about mid-day the patient suddenly developed edema of the lower lip followed rapidly by hoarseness, aphonia and finally dyspnea. One c.c. 1:1000 adrenalin was immediately administered with relief of the dyspnea and aphonia, but the hoarseness persisted. The patient was taken to a field hospital where a laryngoscopic examination was made and edema of both vocal cords seen. On this date there was no generalized urticaria, and the malaise and headache of the day before were now replaced by considerable apprehension. The temperature was not taken. Patient was admitted to the field hospital for evacuation by air to a rear area for further study; he was to leave the following day. In the forenoon of November 15 while sitting on the side of his bed awaiting the arrival of transportation to the plane, the patient sensed the generalized pruritus which presaged the onset of the urticaria and angioneurotic edema. He arose in an attempt to obtain the syringe containing adrenalin but collapsed on the floor of the ward tent in syncope. The male nurse immediately administered 1 c.c. of adrenalin subcutaneously. The patient regained consciousness after a very few seconds and complained of chilliness. Examination at the time revealed extreme pallor and a rapid, thready pulse. Within a few minutes a typical severe shaking chill developed and persisted for about a half hour. Two and a half hours from the time of administration of adrenalin the temperature was found to be 104.6° F. Blood smear for malarial parasites at this time revealed numerous *P. vivax* and combination quinine-atabrine therapy was immediately begun. The patient was evacuated on a stretcher by air three hours later to a station hospital in a rear area.

Family history: Father died at age 43 of pulmonary tuberculosis. Mother, living and well, aged 64. One brother and one sister living and well. History of migraine in the mother, sister, and brother. Sister in past suffered occasional attacks of hives, allergen unknown.

Past history: Usual childhood diseases. Patient has suffered attacks of typical migraine since puberty, approximately four per year. All types of treatment have been tried without success, including an elimination diet.

Patient can recall no previous attacks of hives or other allergic phenomena herein described.

Physical examination at the time of entry into the station hospital: The patient was a fairly well developed white male, age 26, decidedly apprehensive. The sclerae were clear. The nose and throat were normal. The heart showed no abnormality. Blood pressure was 100 mm. Hg systolic and 68 mm. diastolic. No abnormal signs were elicited in the chest. There was an enlarged, tender spleen. The skin was clear.

Clinical course in the station hospital: Anti-malarial therapy was continued as instituted in the field hospital. Difficulty in retaining the medication by mouth was encountered because of severe nausea and vomiting. During the night of November 18 the temperature slowly rose from 100° F. at 1800 to 105.8° at 0400 the morning of November 19. Morphine sulfate was administered and intravenous fluids were begun. Temperature ranged between 101° and 104° through November 19 and fell by lysis on November 21. Nausea and vomiting ceased on November 21, the appetite slowly returned and the condition steadily improved. Anti-malarial therapy was continued in the form of quinine and atabrine for 12 days and atabrine for an additional six days, a total of 18 days. At the time of discharge from this hospital the patient had lost 31 lb. in weight.

Laboratory studies: November 16, 1943. Blood smear showed *P. vivax*.

November 19, 1943. Urinalysis: albumin 2 plus, red blood cells 3 to 6 and white cells 2 to 4 per high power field. Blood: Red cells 4,500,000; white cells 6,000. Differential: polymorphonuclears 66 per cent, lymphocytes 32 per cent, monocytes 2 per cent. Sedimentation rate 26 mm. per hour. Icterus index, 4.

November 20, 1943. Urinalysis: albumin negative. Microscopic negative.

November 24, 1943. Blood: Red cells 3,700,000; white cells 4,700. Differential: polymorphonuclears 54 per cent, lymphocytes 42 per cent, monocytes 2 per cent, eosinophiles 2 per cent.

Subsequent course: Patient returned to the United States and was hospitalized in a general hospital. Weight gain was satisfactory, and there was no recurrence of allergic phenomena or symptoms of malaria. He was discharged to duty March 3, 1944. On March 23, 1944, about mid-day, there occurred the familiar onset of generalized urticaria which was controlled in the manner previously described. Following administration of adrenalin, the temperature rose to 102.4° F. Because the patient was at home on leave no laboratory examinations were made but a complete course of atabrine therapy was taken. There was no further episode of allergy following the initial dose of atabrine. Patient was then in excellent health, doing full duty, until September 6, 1944 when generalized severe urticaria recurred. This was controlled as usual by adrenalin, and the temperature rose to 101.8°. Blood smear taken at this time was negative for malarial parasites but despite this a complete course of atabrine was taken. Patient was entirely well and free from allergic manifestations until October 23, 1944 when again he experienced the sudden onset of generalized urticaria. The urticaria persisted for 12 hours during which time 14 0.5 c.c. subcutaneous injections of 1:1000 adrenalin were required to control the symptoms. On this occasion a new feature was noted: namely, sudden swelling and severe pain in the metacarpophalangeal joints of both hands. Combined quinine and atabrine therapy was immediately instituted with no further recurrence of either the urticaria or malaria to date, an interval of six and one-half months.

COMMENT

The last three recurrences of urticaria and malaria in this case were not proved by positive blood smear. The explanation is that the sensitivity of this patient to the malarial parasite was presumably so great as to result in allergic phenomena 48 hours before the first subjective clinical symptoms of malaria alone

would have appeared and that on the basis of previous experiences, atabrine was instituted 48 hours early thus aborting the usual paroxysm and clinical symptoms such as chills, fever and malaise.

DISCUSSION

In the few described cases of this rare condition, the allergic phenomena invariably accompanied or appeared immediately preceding the fever. The similarity of the sequence of events in the many recurrences of the individual cases conclusively points out the relationship between the malaria and the allergic phenomena. The fact that the latter disappeared on institution of quinine or atabrine therapy equally well rules out the possibility that any quinine or atabrine idiosyncrasy might be responsible for them.

Pathogenesis of the condition is not clear. It has appeared in the presence of both benign tertian and malignant tertian types of infection. The allergic reaction occurs at a time when merozoites are free in the blood stream, thus foreign protein is available to cause an allergic reaction. Probably allergic phenomena are not encountered more frequently in malaria, because of the rarity of the specific sensitivity or susceptibility of the host. The writer has seen approximately 500 cases of malaria with but one instance of specific sensitivity to the malarial parasite. It is apparent that the incidence of the condition is much less than this but no exact figures are available at this time.

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ACQUIRED ARTERIOVENOUS FISTULA WITH COEXISTENT SUBACUTE BACTERIAL ENDOCARDITIS AND ENDARTERITIS*

By SEYMOUR S. CUTLER, M.D., and JULIUS WOLF, First Lieutenant M.C., A.U.S., *Brooklyn, N. Y.*

ACQUIRED arteriovenous aneurysms may result in fatal cardiac insufficiency because of the unfavorable circulatory dynamics set up by the shunt. Another and less common outcome results from the establishment of a subacute bacterial infection of the fistula. This complication has been reported by Bretschneider,¹ Walz,² Gravier,³ Porter and Williams,⁴ Hamman and Rienhoff,⁵ Leaman,⁶ and Touroff et al.⁷ In the first four cases named, there was also a coexisting bacterial endocarditis of the aortic valve. Our case, which has certain unique features, closely resembles the four cases cited and becomes the fifth such to be reported.

CASE REPORT

V. M., a 57 year old Italian longshoreman, was admitted to The Long Island College Hospital June 20, 1944, complaining of generally increasing dependent edema of two weeks' duration. Thirty years before, the patient had been struck by a pistol bullet in the upper anterior aspect of the right thigh. Within a week of the accident, he had noted the presence of a "buzzing," pulsating mass at the site of injury, which had persisted to the present time. Since then he had felt a heavy, dragging sensation in his right leg, and in recent years had noted slight dependent edema and a large chronic ulcerated area on the right shin. Aside from this, he had felt well enough to perform heavy work as a longshoreman until about three weeks prior to his admission. In 1941, the patient had been rejected for life insurance because of a "leaking valve." Since then he had suffered from occasional bouts of palpitation and mild exertional dyspnea. There had been no angina, orthopnea, or paroxysmal dyspnea. For some years he had a chronic non-productive cough, accompanied by substernal discomfort upon coughing.

Three weeks prior to admission the patient suddenly experienced severe pleuritic pain over the right anterior portion of the chest, made worse by the ever-present hacking, non-productive cough, and unaccompanied by hemoptysis. During this time there appeared gradually increasing bilateral dependent edema. At the same time palpitation and exertional dyspnea increased in severity so that the patient was forced to give up work. There were no bouts of angina or paroxysmal nocturnal dyspnea. He experienced drenching sweats at night and believed that his temperature was elevated, though no shaking chills were described. He lost 20 pounds in the two months preceding hospitalization. Past history: He had never had rheumatic fever, chorea, growing pains, joint pains, or scarlet fever. There were no frequent sore throats. He had a left mastoidectomy in 1924 and pneumonia in 1932. There was no history of penile sore, discharge, rash, or exposure to possible sources of venereal infection. The patient was a moderate wine drinker and in addition consumed three bottles of beer daily for many years.

The patient was a well-built, emaciated, pale, middle-aged, white Italian who was cooperative and well-oriented, but obviously ill. He was in the semi-upright position,

* Received for publication September 14, 1945.

From the Department of Medicine, The Long Island College Hospital, Brooklyn, New York.

with rapid and slightly labored respirations. There was no cyanosis of lips or ear lobes, but the skin and sclerae were slightly icteric. There were no spider angiomas. No petechiae were found in the conjunctivae. The fundi were normal. The gums were infected and the teeth were in poor repair. The tongue was rough, the mucous membranes pale. No petechiae were seen. There were violent, bounding carotid pulsations in the neck, but venous pulsations were readily differentiated. There was no nuchal rigidity. The trachea was in the midline and no tug was made out. There was no cervical adenopathy. The thyroid gland was normal in size and consistency. The thorax was very hairy, symmetrical and the expansion normal. Lung fields were resonant throughout, and tactile and vocal fremitus unimpaired, although there were moist râles at both bases. The apical impulse was forceful and diffuse and maximal in the sixth interspace, 14 cm. to the left of the midsternal line. The right border by percussion was 5 cm. from the midsternal line. There was a systolic thrill at the apex which corresponded to a grade V systolic murmur heard over the entire precordium and transmitted to the neck. There was a grade II systolic murmur at the aortic area followed by a dull second sound and a faint blowing diastolic murmur, transmitted to Erb's point. There was a sinus rhythm with rate of 90. Blood pressure was 160 mm. Hg systolic and 58 mm. diastolic in both arms, and both radial pulses were of the sharp, collapsing type. There was a capillary pulse in the fingers. A to-and-fro murmur was heard in the left femoral artery as well as a pistol shot sound. A good dorsalis pedis pulsation was present only in the left foot. There was a large, elongated, pulsating mass, 9 by 5 cm., in the antero-medial aspect of the right thigh beginning 4 cm. below Poupart's ligament. There was no discoloration or venous distention, and there was no difference in temperature between the two thighs. A systolic thrill and bruit were noted over the mass. By pressing the bell of the stethoscope well up under the right inguinal ligament a diastolic murmur and a pistol shot sound, much louder than the corresponding murmurs on the opposite side, were elicited. Immediately above the inguinal ligament, the right iliac artery was twice the diameter of the left, and its pulsations were correspondingly increased. The dorsalis pedis pulsation on the right was markedly diminished. The abdomen was not distended, but there were some dilated cutaneous veins up to the costal margin. There was no fluid wave or shifting dullness. The liver was palpable five fingers'-breadth below the right costal margin. It was hard, smooth, rubbery, and non-tender. A moderately enlarged, firm, easily-displaced spleen was felt in the left upper quadrant of the abdomen. Other organs were not felt, and there was no tenderness or spasm. The genitalia were normal, with no penile scars. There was slight clubbing of the fingers and toes. No splinter hemorrhages, Janeway patches, or Osler's nodes were noted. There was moderate dependent pitting edema bilaterally up to the level of the knees. The right lower extremity was larger than the left. There was a large, depressed, pigmented, atrophic scar, 10 by 5 cm. over the right shin. Over both legs and on the back there were innumerable hemorrhagic spots (1 mm. in diameter) which showed various degrees of fading. The tendon and pupillary reflexes were normal.

On entry there was an erythrocyte count of 2.9 million with a hemoglobin of 10 grams (Haden-Hauser); a leukocyte count of 12,300, with 81 per cent polymorphonuclears, 17 per cent lymphocytes, 1 per cent monocytes, and 1 per cent eosinophiles and a sedimentation rate (Westergren) of 120 mm. per hour. The urine had a faint trace of albumin, a specific gravity of 1.023, and there were positive tests for bile and urobilinogen in the urine. Sediment was negative. The Wassermann reaction was 2+, Kline diagnostic 1+, the Hinton test positive, and the Frei test negative. Blood sugar was 78 mg. per 100 c.c., urea nitrogen 14.8 mg., uric acid 3.5 mg., total protein 8.2 gm., with an albumin of 2.6 gm. and a globulin of 5.4 gm. The icterus index was 14 with an immediate direct van den Bergh of 1.3 mg. per cent; chlorides were 563 mg. The cephalin flocculation test was 4+.

The prothrombin time was 90 per cent of a normal control, and vitamin C 0.4 mg. per 100 c.c. Bleeding time was 2 minutes; clotting time, 3 minutes. The Good-pasture test for solution of blood clot was normal. Electrocardiogram on admission showed a sinus rhythm of 96, PR interval of .16. ST_3 was elevated and ST_1 depressed 1 mm. each; ST_4 depressed 5 mm. with initial deflection downward. There was a left axis deviation. This was interpreted as myocardial disease of the left ventricular strain pattern. On admission, roentgen-ray studies revealed marked calcification and tortuosity of the vessels of the right thigh, hepatomegaly and splenomegaly. There was an elongated aorta, pulmonary congestion, and marked cardiac enlargement both to the right and left.

Course: The patient was placed on a low salt diet with moderate fluid restriction and was started on slow digitalization. Satisfactory diuresis ensued and, in spite of a low grade fever, the patient appeared somewhat better the day after admission. On the fifth hospital day, June 25, the patient experienced a sharp pleuritic-type pain in the right axilla and began to raise a frankly bloody sputum. His temperature spiked to 105° F., pulse rose to 125, and respirations increased to 45 per minute. Bronchovesicular breath sounds and parenchymatous râles were heard in the right axilla. No dullness was demonstrated. A pneumonic infiltration of the right lower lung field was noted by roentgen-ray. Sputum culture yielded *Staphylococcus aureus*, an untypable pneumococcus, *Neisseria flava*, and *Hemophilus influenzae*, all in moderate numbers. Three blood cultures taken June 29, June 30 and July 1 yielded no organisms aerobically or anaerobically; those taken on July 12, July 14 and July 15, each yielded *Streptococcus viridans*, 2 to 4 colonies per c.c., in 10 to 14 days after being taken, six days after the patient's death. Full doses of sulfamethazine were given, and the temperature dropped to an intermittent type of fever ranging between normal and 101.8°. Sulfamethazine levels averaged about 7.0 mg. per 100 c.c. White blood cells numbered 15,000, with 80 per cent polymorphonuclears. Urine showed no additional abnormalities. At this time auricular fibrillation ensued at a rate of 120. The dosage of digitalis was increased, bringing the ventricular rate down to 80. Because of the failure of the sulfonamide to control the fever, penicillin was substituted for sulfamethazine in doses of 15,000 units intramuscularly every three hours. This was continued for five days and discontinued as the patient was afebrile but still showed no subjective or objective signs of improvement.

At this time further investigation of the arteriovenous fistula was undertaken. Obliteration of the shunt by manual pressure caused an immediate rise in systolic blood pressure of 40 mm. of mercury (Branham phenomenon), without significant decrease of the pulse rate. This failure to slow the pulse was probably due to the inactive carotid sinus reflex. A control procedure on the left side changed neither the systolic blood pressure nor the pulse rate. From this time until death the patient had a remittent type of fever from 99° to 101° F. There appeared numerous crops of tiny hemorrhagic spots similar to those previously described. Urine sediment remained free from red blood cells until the last few days of life, at which time a rare red blood cell per low power field was found. No splinter hemorrhages or petechiae were found on the mucous membranes. The icterus index increased to 24; total protein was 8.2, gm., with an albumin of 1.6 gm. and a globulin of 6.6 gm. The arm to lung circulation time was 23 seconds (ether); venous pressure was 150 mm. of saline on July 17. A prothrombin time on this date was normal. During the last week of life, the patient complained of generalized abdominal pain. The abdomen was distended and tympanitic; free fluid was demonstrated. On the last day of life, abdominal pain and distention increased greatly, the temperature spiked to 103° F., and the respirations increased to 60. Wangensteen suction, repeated Harris drips, neostigmine and morphine were useful in decreasing the distention. However, the patient lapsed into coma, and in spite of supportive therapy, died on the twenty-eighth hospital day.

Pathological Report. An autopsy was performed by Dr. Jean Oliver nine hours after death.

Gross: The peritoneum over all the abdominal viscera was intensely congested and bright red, an appearance which apparently was due to a great number of small confluent petechial hemorrhages. The liver projected about 2 fingers' breadth below the costal margin. The external surface was roughly granular.

The heart was about two and a half times the size of the fist, weighing 720 grams. The left side was enlarged and quite firm. The right ventricle was even more greatly enlarged and was filled with postmortem clot and fluid blood. The tricuspid orifice admitted three fingers and the mitral orifice the tips of three fingers. The mitral valves were quite smooth and showed an occasional yellow atheromatous spot. Attached to all three of the aortic valves at about the center of each flap were soft, irregular vegetations measuring roughly 2 mm. to 5 mm. in diameter. These vegetations covered ulcerations in the valve flap. The remaining valve flap tissue was definitely thickened and in the posterior cusp at its base was a mass of calcareous material about 2 mm. in diameter. The orifice of the left coronary artery was widely patent. Its course was tortuous, and there were some atheromatous plaques in its wall. The right coronary was also very tortuous and its walls were thickened, but there was no apparent interference with the lumen of either vessel. The aorta lay in its usual position and was of normal calibre.

The intima of the aorta was quite smooth above the valve. In the upper thoracic portion were a moderate number of atheromatous spots and plaques. These increased in frequency in the abdominal portion of the vessel and there showed calcification and some ulceration. There were no recent evidences of splenic infarction. The liver weighed 1660 grams and measured 24 by 16 by 9 cm. The left lobe was deformed by superficial scars which extended a slight distance below the surface of the organ. On the cut surface there was marked jaundice of the hepatic tissue and an irregular mottled pattern due to extreme irregular congestion of the parenchyma.

The left common iliac artery arose in a normal manner and passed down into the pelvis in its usual way. At its origin it was 2.75 cm. in circumference. Its wall was thick. The right common iliac artery was considerably dilated at its origin, the circumference measuring 5.5 cm. Its wall was also thickened and showed scattered atheromatous plaques and some small ulcers. Two cm. below the exit of the ileolumbar artery the right external iliac suddenly dilated into an irregular saccular cavity whose greatest dimension was about 8 cm. An irregular series of dilatations extended for about 13 cm. down the course of the artery, so that the tortuous vessel lay along the brim of the pelvis and was covered and bound down by a mesentery-like fold of peritoneum. The wall of these aneurysmal sacs was less than 1 mm. in thickness and contained thin calcified plates. Below the saccular dilatations just described the femoral artery passed into Hunter's canal and again assumed its former diameter of about 5 cm. Here the wall was quite thick. At a point 13 cm. below the last aneurysmal sac mentioned above and 4 cm. below the exit of the profunda femoris was another single aneurysm which measured 7 cm. in diameter and 8 cm. in length. Its wall was quite thin and in part calcified. Below this second aneurysmal sac the femoral artery was reduced in diameter to about 2 cm. and was heavily calcified. Just below the lowermost aneurysm was an orifice in the wall of the artery, 1 cm. in diameter, which led to a communication that passed upward and back to the femoral vein. At the point of junction of vein and artery there was a calcareous mass 1 cm. in diameter covered and infiltrated with thrombotic material. From this point on, the femoral artery proceeded downward in its usual course. The profunda femoris arose in its normal position. It passed through a mass of dense connective tissue scar in a tortuous course. Its wall was thickened and calcified. No single venous trunk was found below the communication between artery and vein. Several large

veins joined, however, to form a femoral vein which lay in its usual relation to the artery. The vein was greatly and irregularly dilated, some stretches measuring only 2 cm. in diameter and others forming pouch-like varices 20 cm. in diameter. At its junction with the common iliac the vein was 7 cm. in diameter. In spite of the stretching the wall was thick and normal valves were seen in it.

Microscopic: Ventricle: The muscle fibers throughout the section showed a moderate increase in size. The nuclei were well stained, and there was no evidence of necrosis. The small arteries showed in general a definite thickening of their walls, but the connective tissue about them in most cases was free of inflammatory cells. Occasionally, however, in the periarterial regions were collections of mononuclear cells and large irregular cells with large, clear, oval nuclei and a prominent nucleolus. In some instances these cells were arranged in nodule-like clusters that included part of the wall of the small artery.

Aortic Valve: Sections showed a marked hyaline thickening of the valve tissues. There was extensive destruction of this fibrous tissue, and on its surface was a large thrombus in which masses of bluish-staining bacteria might be seen. Apart from the septic thrombus, there were other small fibrinoid nodules which showed no bacteria. Beneath these the valve tissue was filled with large irregularly shaped cells, many with more than one nucleus. The nuclei were large and vesicular and had prominent nucleoli. None of these cells was found about the base of the mitral valve or in the region of the annulus fibrosus. Gram stain showed occasional small chains of diplococci in the septic thrombus. The aorta showed a hyaline thickening of the intima to a moderate degree. The muscle of the media was well preserved.

There was a marked fibrous thickening of the capsule of the liver, and from this thickened capsule bands of connective tissue ran down into the parenchyma of the organ for a considerable distance. There was a moderate increase in the connective tissue in the peri-portal regions and in some places a considerable round cell infiltration. The capillaries between the hepatic cords in many areas showed a marked dilatation with atrophy of the hepatic cells. This passive congestion was more pronounced near the surface of the organ.

Small Intestine: There was a marked edema of the submucosa, muscularis and serosa. In the edematous tissue were scattered leukocytes, both mononuclear and polymorphonuclear. Beneath the serosa there were many red blood cells, and a relatively lesser number of leukocytes. Gram stain did not show any bacteria.

COMMENT

Many of the changes in cardiovascular dynamics due to arteriovenous fistulae have been understood since the time of William Hunter (1757), but the studies of Emile Holman and his coworkers have clearly defined and elucidated these changes.^{8,9} There is now general agreement that in the presence of a moderate or large arteriovenous fistula of appreciable duration, the following changes occur: (1) Increase of circulating blood-volume. (2) Increase in cardiac output. (3) Increase in pulse pressure. (4) Hypertrophy and dilatation of the heart. (5) Increased local venous pressure both proximal and distal to the fistula. Presumably, a generalized rise of venous pressure does not occur until cardiac insufficiency supervenes.

In addition to the general circulatory changes that result from an A-V fistula, certain localized alterations of the aortic valves are of prime importance because these changes supply the nidus for the later development of a bacterial endocarditis. In this case, because of the absence of the commoner endocardial altera-

tions due to rheumatic, syphilitic or congenital heart disease, minor benign changes of the heart valves are thrown into prominence.

Gouley and Sickel¹⁰ have recently described a characteristic lesion of the aortic valve occurring in cases of aortic regurgitation resulting from stretching of the aortic ring. "This lesion is a sclerotic thickening confined to the mid-portion of the free edge of the aortic leaflets. It is essentially a loss and fibrous replacement of the original corpora arantii, without involvement of the lateral portions of the free margin of the leaflet or of the body of the leaflet, except insofar as marked central involvement necessarily extends some distance toward the periphery." Together with this marginal fibrosis, Gouley and Sickel describe elongation of the aortic leaflets with deepening of the sinuses of Valsalva and dilatation of the aortic ring (greater than 7.5 cm.). The aortic valve commissures of some of their cases were stretched apart without loss of the sharpness of the adjoining

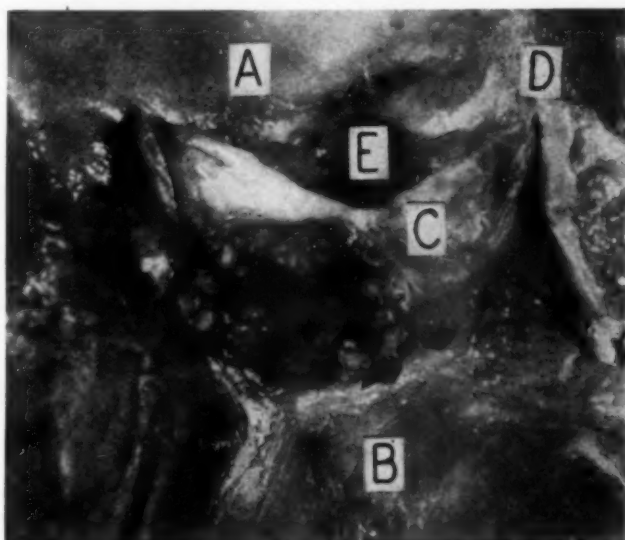


FIG. 1. Aortic valve. A—left atrium; B—left ventricle; C—left posterior valve cusp with its ulcerating vegetation; D—commissure. Note the sharpness and the lack of widening and overgrowth. E—deepened sinus of Valsalva.

free margins of the valves. This change is said to be quite distinct from the overgrowth and extension of syphilitic aortitis into the commissures. It will be noted that the marginal sclerosis resembles the rolled cord-like edge of the syphilitic aortic valve, which is not surprising if the underlying cause of the valve changes in both types of regurgitation is the dilatation of the aortic ring. Even those cases of hypertensive heart disease which exhibit this valve change without dilatation of the aortic ring, as measured at necropsy, may fall into this classification in view of the tremendous "dynamic dilatation" of the aorta present during life. The aortic valves in our case (figure 1) presented the changes described above. The lengthening of the valve leaflets, the depth of the sinuses of Valsalva and the sharp edges of the commissures are clearly demonstrated. The aortic ring measured 9.5 cm. in circumference, and the base of the arch was entirely free

from the changes typical of syphilitic aortitis. We believe that this aortic valve was not the seat of syphilitic infection in spite of the positive serological tests for syphilis because of the absence of the diagnostic gross and microscopic features of this condition—destruction of the medial elastic fibers of the aorta, dilatation, fine wrinkling and coarse scarring of the intima, thickening of the adventitia, widening of the commissures, perivascular inflammation and necrotic mesaortitis. We believe that the aortic valve was not the seat of rheumatic infection because of the lack of valvular scarring and distortion. We feel that the collections of atypical mononucleated cells scattered throughout the myocardium are not true Aschoff bodies but are the “wandering mononuclear cells” seen in subacute bacterial endocarditis. Credence is lent this view by the relative scarcity of these cells at the base of the mitral valve, the location where these cells are most numerous in rheumatic carditis.^{11, 12}

Our reconstruction of the pathogenesis, therefore, is as follows: The bullet wound established at least a moderate sized fistula as judged by the presence of a “buzzing, pulsating mass” easily perceived by the patient. During the next three decades, marked hypertrophy and dilatation of the heart appeared. The resultant stretching of the aortic ring was for a time compensated by the lengthening of the aortic valve leaflets, but eventually, aortic insufficiency ensued. As a result of the high pulse pressure, with forceful snapping of the supple leaflets at the onset of each diastole, hypertrophy of the corpora arantii and the changes described by Gouley and Sickel occurred. Cardiac insufficiency set in, and finally, *Streptococcus viridans* became implanted upon the aortic valves and the margin of the fistula, and subacute bacterial endocarditis and endarteritis were established. The oral sepsis may have provided the source for the blood stream infection.

Our case presents a number of points of considerable clinical interest. Among these are the jaundice, the positive serological tests for syphilis, the pattern of atherosclerosis, and a capillaritis of the skin and serosa. The patient was icteric throughout his hospital course. The liver was palpable five fingers' breadth below the costal margin and the spleen was easily felt in the left upper quadrant. Liver function tests indicated impaired function. Cephalin flocculation was 4; albumin was depressed to 1.6 gm. with a globulin of 6.6 gm. (Frei test was negative). These facts together with a history of consumption of wine and beer for many years led us to believe that a cirrhosis of the liver was present, which was made more severe by the long-standing anoxemia due to chronic passive congestion.^{13, 14} On necropsy there was noted scarring of the liver with moderate increase of periportal connective tissue. The patient therefore had early cirrhosis of the liver, which, aggravated by the passive congestion, further increased the difficulty of diagnosis.

The positive Wassermann and Hinton tests were also of more than passing interest. In retrospect, we feel that since there was no pathological evidence of syphilis, the serological tests for syphilis were false positives due either to the jaundice, to the endocarditis, or to hyperglobulinemia, although latent syphilis cannot be absolutely ruled out. The fact that the titers were low lends further support to this belief. Hyperglobulinemia may cause false positive serological tests for syphilis, and, in this case, is the probable cause for these reactions. The hyperglobulinemia may have been due to the cirrhosis as well as the subacute bacterial endocarditis.

It will be seen in figure 2 and in the gross pathological description that the right common iliac, external iliac, and femoral arteries are considerably dilated and tortuous as compared with the normal left-sided vessels. In addition to this obvious expression of increased blood flow, there is also a tremendous increase in the amount of atheromatous change and ulceration of the intima on the affected side. It has been stated¹⁵ that there is an increased tendency to the deposition of



FIG. 2. A—abdominal aorta; B—right common iliac artery, and below, right external iliac artery; C—left common iliac artery; D—femoral arterial aneurysms; E—femoral artery.

cholesterol in the walls of vessels subjected to marked turbulences, eddy currents, rapid changes of pressure, or other changes which may set the walls vibrating. If this is true, the extensive change of the affected vessels need not surprise us.

The purpuric eruption noted during life over the legs and back was of considerable interest in view of the normal prothrombin, plasma and vitamin C levels, and the normal Goodpasture test. The parietal peritoneum and the serosa

of the small intestines were found at autopsy to be "bright red" owing to innumerable, densely scattered petechial hemorrhages. This finding is thought to be an unusual response of the capillaries to the streptococcal proteins.

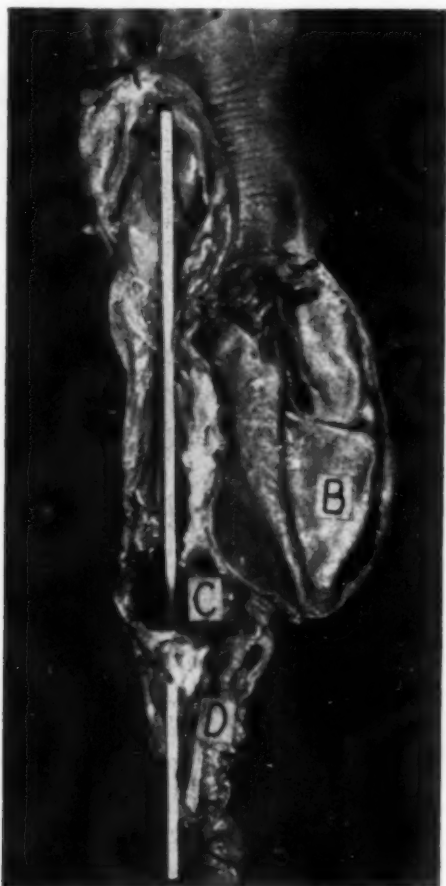


FIG. 3. A—femoral artery (proximal); B—arterial aneurysmal sac; C—infected thrombotic material; D—femoral artery (distal); the probe lies in the femoral vein, and passes through the arteriovenous fistula between C and D. Note: The arteriovenous aneurysm shown in figure 3 is distal to, and connected with the multiple arterial aneurysms seen in figure 2 by normal femoral artery, E in figure 2.

CONCLUSIONS

1. This is the fifth reported case of acquired arteriovenous aneurysm of the femoral artery and vein, complicated by subacute bacterial endocarditis of the aortic valve and by bacterial endarteritis of the fistula.
2. The aortic valve was the seat of a "mechanical sclerosis" similar to that in hypertension, thus supplying the nidus for the endocarditis.
3. Other findings of clinical interest are noted and discussed.

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**PAROXYSMAL VENTRICULAR TACHYCARDIA: REPORT OF
A CASE SHOWING THE PHASES OF RECOVERY
RECORDED BY ELECTROCARDIOGRAPH ***

By JAMES A. COLLINS, JR., M.D., Danville, Pennsylvania

THE uncommon finding of paroxysmal ventricular tachycardia with the phases of recovery recorded by electrocardiograph prompted this communication. The usual prognosis in such a case is quite grave, and since this patient recovered under therapy in spite of serious myocardial damage, it was thought worth while to report it.

CASE REPORT

W. E., a white male, aged 64, was admitted to the hospital by ambulance. He had suffered from a severe attack of precordial pain two years previously. The pain

* Received for publication August 6, 1945.

From the Department of Medicine, Geisinger Memorial Hospital, Danville, Penna.

radiated down the left arm and was accompanied by dyspnea, weakness, and perspiration. Apparently, this was a coronary occlusion, although it was never proved. Following his recovery, there was persistent angina pectoris on slight exertion, dyspnea, and weakness. The present illness began two days prior to admission. It was characterized by excruciating, vice-like chest pain, marked dyspnea, and weakness. A hypodermic given by his local physician relieved the pain, only to have it return again in a few hours. The patient was then referred to the hospital for further treatment, the provisional diagnosis being acute coronary occlusion.

The physical examination revealed an elderly male, critically ill. He was markedly dyspneic, orthopneic, and cyanotic. The temperature was 98°, respirations 28 and blood pressure 82 mm. Hg systolic and 40 mm. diastolic. The cardiac rate was 200 to 250 at the apex and only 60 at the wrist. The mouth showed poor dental hygiene, and there was chronic infection of the pharynx. The veins of the neck and

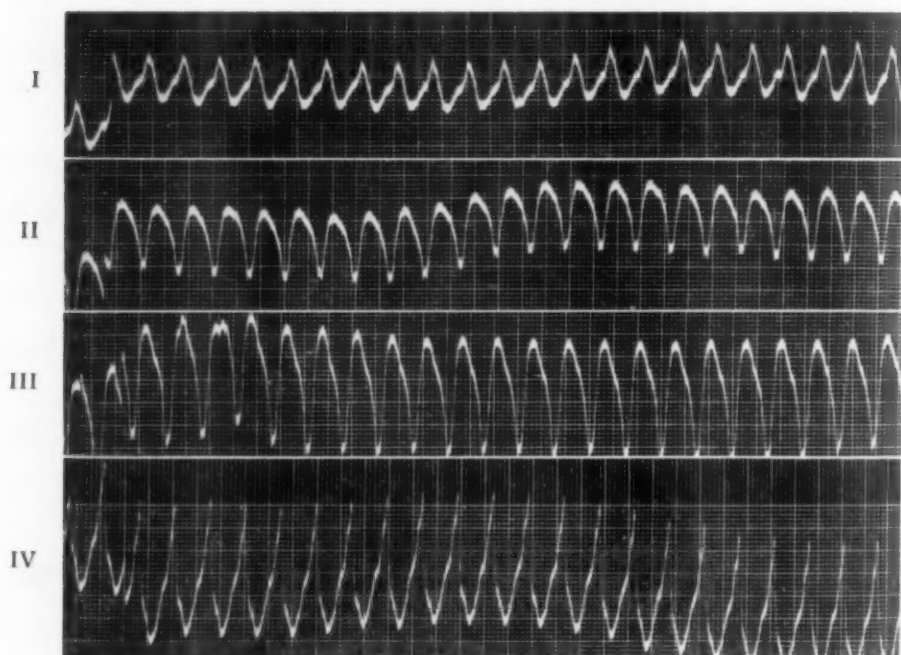


FIG. 1. Ventricular tachycardia, rate 196, taken on admission.

chest were distended, and pulsations were quite prominent. The lungs were relatively clear. The heart was not enlarged, and the rhythm was considered regular. There were no audible murmurs. The liver was palpably enlarged and tender, and the abdomen was distended with gas. Peripheral vessels revealed a moderate degree of sclerosis. There was no peripheral edema.

The urinalysis and blood count were both entirely normal, with 6350 leukocytes. The blood Wassermann reaction was negative. A portable electrocardiograph taken shortly after admission showed ventricular tachycardia (figure 1). Treatment consisted of strict bed rest, intranasal oxygen, at first morphine, and later papaverine. Digitan was administered intramuscularly for one dose, then digitalis was given daily, grains 1½, for three additional days. Quinidine sulfate was started the day after admission, with a dose of 5 grains every two hours. This was increased to 15 grains

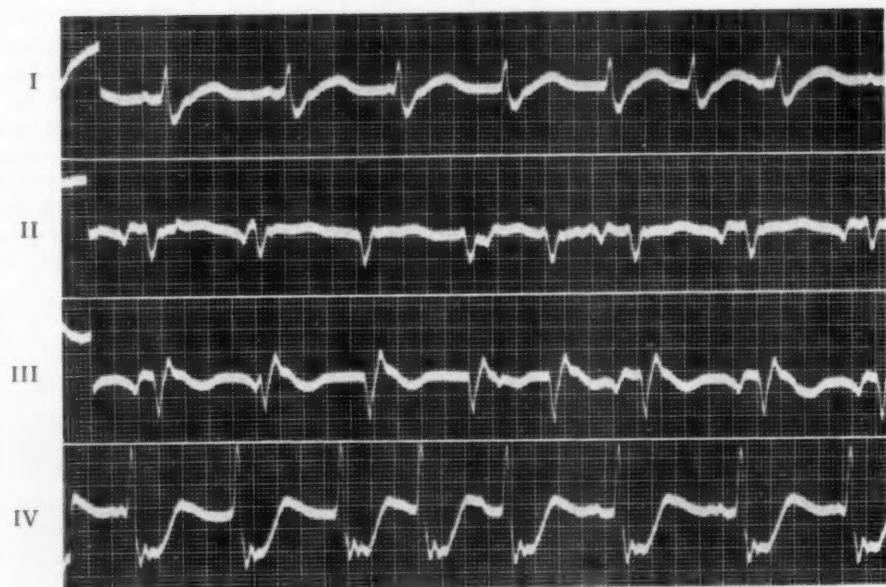


FIG. 2. Complete heart block with irregular ventricular beat, rate 67. Probable recent coronary occlusion, sixth hospital day, after quinidine therapy.

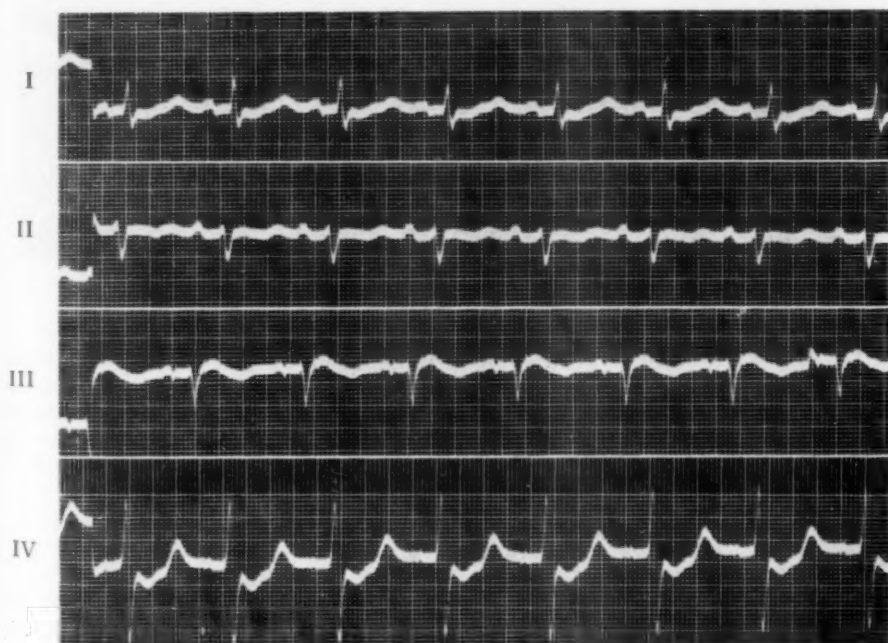


FIG. 3. Sinus rhythm, first degree heart block. Rate 65, seventh hospital day.

every two hours for five doses daily until a total of 210 grains had been administered within 80 hours. Digitalis was discontinued at this point. Throughout all this medication, there was no appreciable change in cardiac rate or status. The day after discontinuing digitalis, while continuing quinidine, the pulse rate became quite slow, recorded as 60. An electrocardiographic tracing revealed complete heart block with an irregular ventricular beat, and also T and RT changes compatible with a recent coronary occlusion (figure 2). This was the sixth hospital day. On the seventh hospital day the cardiac rate was regular, no pulse deficit was present, and the electrocardiograph indicated sinus rhythm, first degree heart block, and coronary occlusion (figure 3). Digitalis was given in place of quinidine, because neither quinidine sulfate nor hydrochloride was available at the time the patient was admitted.

The patient progressed through a normal convalescence for the next week in the hospital without any further cardiac difficulty. He was discharged then to continue his convalescence at home.

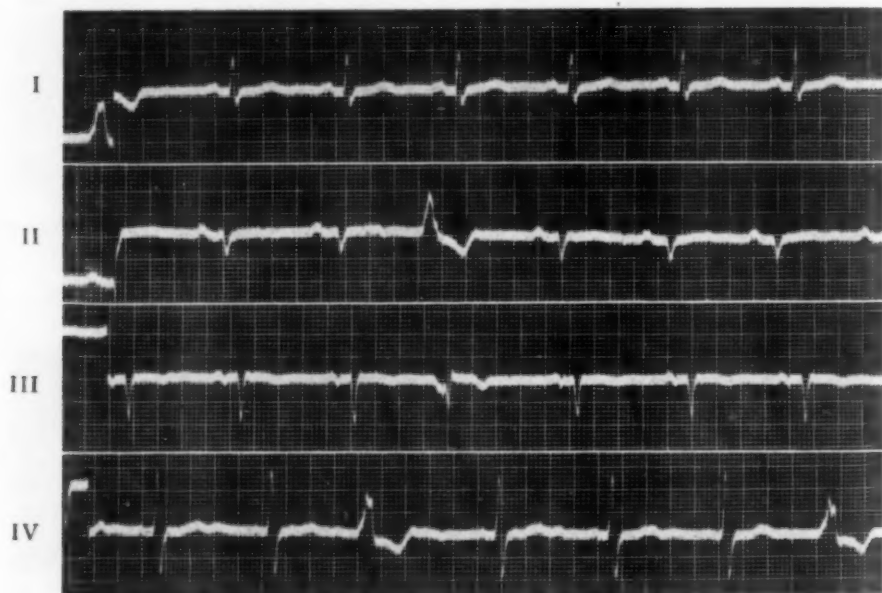


FIG. 4. Ventricular premature contractions. Rate 60, six months later.

The patient returned for a follow-up visit six months later. At this time, he had no serious complaints referable to the cardiovascular system. The examination of the heart showed an irregular rhythm, sounds of fair quality with no murmurs heard. An electrocardiogram at this time revealed ventricular premature contractions with considerable myocardial damage. The T-waves were compatible with an old myocardial infarction (figure 4).

SUMMARY

A case of rapid ventricular tachycardia associated with recent coronary occlusion is reported. The rhythm progressed through ventricular tachycardia, complete heart block, first degree heart block, and normal sinus rhythm under treatment. The treatment consisted of heavy doses of quinidine sulfate, 15 grains

every two hours for 10 doses; and later five grains three times a day after cessation of the ventricular tachycardia. It is believed that digitalis is contraindicated and tended to maintain the tachycardia. It was after discontinuing digitalis that the effect of the quinidine was manifest. The tachycardia continued throughout eight days with no abatement, but ceased shortly after all digitalis was discontinued, while quinidine therapy was continued.

CONCLUSIONS

1. Quinidine sulfate is the drug of choice in the treatment of ventricular tachycardia.
2. Digitalis is harmful and acts against the effect of the quinidine sulfate in the treatment of this condition.
3. Rather large doses of quinidine sulfate are tolerated, apparently without much difficulty.

EDITORIAL

BAL IN THE TREATMENT OF ARSENIC AND MERCURY POISONING

THE term BAL is a contraction for British Anti-Lewisite, a compound developed by Peters, Stocken, and Thompson¹ during the recent war as an antidote to the arsenical blister gases. The chemical name for BAL is 2,3-dimercaptopropanol. First intended for the local decontamination and treatment of the skin and eyes, this compound was subsequently found to be effective in the systemic treatment of severe arsenic poisoning, not only after exposure to the arsenical blister gases but also when this occurs as a complication of arsenotherapy. More recent experimental and clinical observations have demonstrated that BAL exerts an equally striking protective and therapeutic effect in mercury poisoning.

In order to make available the research work which is the basis for the therapeutic use of BAL, a committee, consisting of representatives of the various groups which had participated in the BAL study, was appointed to plan and carry out publication of the experimental data. Under the chairmanship of Dr. Warfield T. Longcope, the committee decided that papers on the fundamental work on BAL be selected and divided into three groups: those dealing with biochemistry, those dealing with toxicology, and those dealing with clinical applications. The British *Biochemical Journal*,² the *Journal of Pharmacology and Experimental Therapeutics*,³ and the *Journal of Clinical Investigation*⁴ were considered to be especially suitable for publishing the papers selected in the form of a symposium.

There is now a convincing body of evidence that the toxic effects of arsenicals are referable primarily to the fact that they combine with -SH groups in the tissues and thus block one or more physiologic systems critical to the cellular economy. It was further shown that these toxic effects were not only prevented but could actually be reversed by -SH compounds. The implication that the toxic action of arsenicals is referable to the inactivation of -SH-containing enzyme proteins in living cells is clear.

Simple dithiol compounds form relatively stable ring compounds with Lewisite and other trivalent arsenicals. Of the various dithiols tried out BAL, or 2,3-dimercaptopropanol, recommended itself particularly as a local decontaminant in combating the arsenical blister gases when applied to the skin or eyes in ointment form. The action of BAL is ascribed to the fact that, by reacting with arsenicals to form a stable ring compound, it can effectively compete for the arsenical with the thiol groups of tissue proteins.

¹ PETERS, R. A., STOCKEN, L. A., and THOMPSON, R. H. S.: British Anti-Lewisite (BAL), *Nature*, 1945, clvi, 601.

² *Biochem. Jr.*, 1946, xl, 513—6 articles.

³ *Jr. Pharm. and Exper. Therap. (Supplement)*, 1946, lxxxvii—125 pages—15 articles.

⁴ *Jr. Clin. Invest.*, 1946, xxx, 451—11 articles.

This competition involves two distinct processes: (1) combination with the toxic arsenical before it combines with tissues; (2) removal of arsenic from the tissues after it has already combined, with the formation of BAL-thioarsenite from the tissue protein-thioarsenite and the release of the tissue thiol groups.

BAL, administered topically, subcutaneously, intramuscularly, or intravenously to animals, exerted both protective and therapeutic effects against local and systemic injury by toxic arsenicals. Toxic side-effects from effective doses were not serious in the experimental animals; hence it seemed safe to proceed with cautious trials of BAL therapy in patients with arsenical poisoning.

Pharmacologic observations and toxicity studies on BAL in man revealed the following points of interest: Atopical application of BAL in the form of a 5 per cent ointment is safe, although it may cause local irritation. Skin sensitization to BAL developed in only 19 per cent of the individuals tested when the ointment was applied to normal skin, but in 66 per cent when the ointment was applied to damaged (burned) skin. Parenteral administration of up to 5 mg. per kilogram every four hours for four doses will produce no lasting damage in the average normal individual, although certain transitory toxic effects were noted in many instances. These toxic effects consisted of paresthesias, perspiration and a sense of warmth, pains in the limbs, jaws, abdomen, and head, lacrimation, blepharospasm, salivation, vomiting, unrest, apprehension, weakness, fatigue, tachycardia, and transitory hypertension. The minimal dose producing toxic effects lies between 3 and 5 mg. per kilogram. A 10 per cent solution of BAL in peanut oil and benzyl benzoate proved to be most satisfactory for intramuscular administration. In normal men and those exposed to minimal quantities of an arsenical smoke a single injection of BAL in dose of 3 to 5 mg. per kilogram was regularly followed by a significant increase in the rate of urinary arsenic excretion.

Reports from both England and this country attest to the beneficial effects of both topical and parenteral administration of BAL in the treatment of arsenical dermatitis. Victims of intractable localized dermatitis caused by diphenylamine chlorarsine improved rapidly with the application of BAL ointment, which was, however, quite painful when applied to the inflamed skin. Since intramuscular injections were much less disturbing, this route of administration soon became the preferred method of treatment. Patients with exfoliative dermatitis from antisyphilitic arsenicals improved with either local or parenteral therapy. The duration of the dermatitis was distinctly shortened, although mild recurrences were frequent if treatment was not continued for at least one week. With an average intramuscular dose of 300 mg. per day, no serious constitutional reactions were encountered. The English workers report no significant change in the excretion of arsenic that could be attributed to BAL in their dermatitis patients, whereas the American group found a consistent increase in arsenic excretion after BAL therapy of arsenical dermatitis, corresponding to the good clinical response of these

patients. No such regular improvement was evident, either clinically or in the excretion of arsenic, after BAL therapy in jaundiced patients with toxic hepatitis attributed to arsenical poisoning.

Eagle⁵ in summarizing clinical experience with BAL reports that this compound has been used in more than 200 cases of various types of arsenic poisoning with results that indicate that the danger of some complications may be markedly reduced by its early administration in adequate dosage. He concludes that BAL must be given early in somewhat larger doses than were originally recommended. In the severe complications, a dose of 3 mg. per kilogram should be injected every four hours for the first two days followed by a similar injection every six hours on the third day and twice daily thereafter for two days, or until complete recovery. In 88 cases of arsenical dermatitis, 51 being typical exfoliative dermatitis, definite improvement was noted in 80 per cent of the exfoliative cases within three days with complete recovery within an average of 13 days. In 55 patients with hemorrhagic encephalitis caused by intensive arsenotherapy, 40 of whom were either convulsing or comatose when BAL was given, recovery followed in 44 within one to seven days. Ten of 11 patients with arsenical agranulocytosis recovered under BAL therapy; increase in the total white blood cell count and an even more pronounced increase in polymorphonuclears was usually apparent within two days, and the white count approached normal within one week. On the other hand, BAL in the dosage used had no effect in three cases of aplastic anemia occurring as a complication of arsenotherapy. Although the clinical response of jaundiced patients to BAL was less dramatic, the symptomatic improvement in five of 14 cases was so prompt that it appeared to be due to the use of BAL. Of four patients who were erroneously given a massive overdose of mapharsen, the three who received prompt and adequate treatment recovered rapidly.

Pertinent to the background of the study of the effects of BAL in mercury poisoning were the observations supporting the general hypothesis that other heavy metals besides arsenic are toxic to biological systems because of their reaction with SH groups of the protein moiety of cellular enzymes to form mercaptides. Mercury shares in this action and BAL has been shown to be capable of reactivating enzyme systems poisoned by mercury. In experimental animals BAL exerts a striking protective action from poisoning by bichloride of mercury given orally or intravenously. Remarkable protection was noted in dogs even if the administration of BAL was delayed for two to five hours after the oral administration of otherwise lethal doses of mercury.

On the basis of the encouraging results noted in experimental animals, a clinical study of the effects of BAL in mercury poisoning was instituted by Longcope and his associates. Twenty-three patients suffering from bichloride of mercury poisoning were treated by intramuscular injections of BAL with only one death, although 15 of these patients had ingested sufficient

⁵ EAGLE, H.: The systemic treatment of arsenic poisoning with BAL (2,3-dimercaptopropanol), Jr. Vener. Dis. Inform., 1946, xxvii, 114.

mercury to have been lethal in a high percentage, had no specific treatment been administered. A total of 450 to 750 mg. were injected during the first 12 hours with a total dosage of 900 to 2870 mg. over the first three or four days. Considerable importance was attached to the prompt treatment by BAL in an initial injection of 300 mg., followed within the first 12 hours by two or three further injections of 150 mg. each. Toxic effects of BAL were observed in a few patients. Perhaps the most significant effects of treatment were the prompt relief of even the most alarming symptoms, when BAL in sufficient doses was administered within three to four hours after the bichloride of mercury had been swallowed, and the rapidity with which the patients made a complete recovery. In the only fatal case in the series, treatment could not be started until 13 hours after the ingestion of the poison. In the same paper the authors mention briefly 19 additional cases of bichloride poisoning treated with BAL with only one death, or a total of 42 patients treated with only two deaths! These figures speak for themselves in acclaiming the truly miraculous protective action of BAL in clinical mercury poisoning.

So much for the remarkable antidotal action of BAL in the treatment of arsenical and mercurial poisoning. Experimental work suggests that this chemically simple dithiol may prove to be equally effective in the prevention or treatment of poisoning from other heavy metals. War is rightly regarded by civilized man as an unmitigated evil, but, if there is any consolation to be gained therefrom, it lies in the tremendous impetus given to scientific research, both medical and non-medical, by the war-time emergency such as resulted in the discovery of BAL. The many chemists, pharmacologists, and clinicians—far too numerous to mention all by name—who collaborated in this discovery and its important applications are surely to be congratulated on a good job well done.

W. H. B.

REVIEWS

Ambulatory Proctology. By ALFRED J. CANTOR, M.D.; foreword by BEAUMONT S. CORNELL, M.D. 524 pages; 14.3 × 20.9 cm. Paul B. Hoeber, Inc., New York, N. Y. 1946. Price, \$8.00.

The author presents a valuable discussion of the diseases of the colon, rectum and anus. As indicated in the title, the book stresses ambulatory treatment. In the opinion of the reviewer many of the procedures recommended for office practice should not be attempted outside of a hospital except perhaps by an experienced proctological surgeon with exceptional equipment and assisting personnel in his office.

T. R. A.

The Modern Treatment of Diabetes Mellitus. By WILLIAM S. COLLENS, B.S., M.D., and LOUIS C. BOAS, A.B., M.D. 514 pages; 15.5 × 23 cm. Charles C. Thomas, Springfield, Illinois. 1946. Price, \$8.50.

The authors present their book as "a practical comprehensive guide for the general practitioners who treat diabetic patients" and it contains a great deal of information on dietary and insulin therapy of the disease.

The diagnostic aspects of the disease are discussed briefly and the major portion of the book concerns itself with treatment. Diabetes mellitus is classified according to the severity of the disease, the nutritional status of the patient and the presence or absence of acidosis. Detailed descriptions of the diets to be employed for the various types of the disease with methods of calculation and clock-like diagrams showing hours of feeding and insulin administration are clearly presented. The complications are discussed under their different headings and the discussion and illustration of degenerative disease of the peripheral arteries are well presented. Thirty-five pages are devoted to laboratory procedures and technics of insulin administration. Included with the book is a Collens Diet Calculator which is intended to simplify diet-writing.

This book is a well organized presentation of the treatment of diabetes mellitus. It should prove a valuable guide to the many physicians who are faced with the multitude of problems that may arise in the treatment of this disease.

J. Z. B.

The Venereal Diseases. By JAMES MARSHALL, M.B., B.S., M.R.C.S., L.R.C.D., Major R.A.M.C., Command Venereologist to the Eastern Command and London District. 348 pages; 14.5 × 22 cm. Macmillan & Co., London. 1946. Price, \$4.50.

The author has presented his subject in a manner which does not conform to the methods used in this country. The chapters on gonorrhea give only brief mention of the necessity for cultural proof of cure, and great stress is laid on the chemotherapy of the disease, but mention of the use of penicillin is omitted. This latter omission may be due to the fact that at the time that this book was written, penicillin did not enjoy the wide use that it does at the present time. No mention is made of the necessity for routine serologic tests for syphilis in the treatment of patients for gonorrhea. The description of the course of the disease in men, women, and female children is adequate. These chapters dealing with the treatment of syphilis are now outdated due to the almost universal use of penicillin. At the time this book was written evidently mapharsen was infrequently used in Great Britain, and the author

speaks of it in disparaging terms. The subjects of chancroid, lymphogranuloma venereum, and granuloma inguinale are very briefly covered in six pages of the text. Unfortunately, this book cannot be recommended as a guide for students or practitioners in the United States.

H. M. R., JR.

The Medical Value of Psychoanalysis. By FRANZ ALEXANDER, M.D. 278 pages; 21 × 15 cm. W. W. Norton Co., Inc., New York. 1936. Price, \$3.00.

This book, by one of the leaders of psychoanalysis in this country, although published ten years ago, is still up-to-date and very timely. It will have especial appeal to those who are currently interested in psycho-somatic problems. It is written in clear, understandable language and the conclusions presented are well supported by careful studies. The content of the book concerns itself with the development, theory and implications of psychoanalysis. Extravagant claims are carefully avoided. The most useful chapter describes how recent researches have improved our understanding and treatment of such conditions as: Duodenal ulcers, gastric neurosis, mucous colitis, chronic constipation, essential hypertension and other similar problems. Many stimulating suggestions are made regarding the problems that need to be further studied. The author also makes suggestions for improving the medical student's understanding of psychogenic factors in disease.

H. W. N.

The Examination of Reflexes. A Simplification. By ROBERT WARTENBERG, M.D. Foreword by FOSTER KENNEDY, M.D. The Year Book Publishers, Inc., Chicago. 1945. 222 pages; 18.5 × 12.5 cm. Price, \$2.50.

"Again and again in my teaching," the author states, "I have been impressed by the confusion of the student as he struggles with the multitudinous reflexes and their chaotic nomenclature. These studies on reflexes were undertaken primarily with the idea of offering him a simple and comprehensive review of the reflexes in their relation to practical neurologic diagnosis. This entire study is based on and developed from a few fundamental theoretic postulations on the physiologic nature of the muscle stretch reflexes."

"The time of purely descriptive symptomatology is over," the author says at another point. "Modern neurology needs and wants more physiologic orientation. Every new observation in clinical neurology should be subjected to a strict physiologic interpretation."

These quotations sum up the purpose and the basis of the studies presented in this book. The author interprets the deep reflexes uniformly as muscle stretch reflexes. "The muscle reacts to . . . sudden stretching (through a sudden, brief concussion) with contraction, which constitutes what is called the deep, or tendon, reflex." The author distinguishes from them such reflex phenomena as associated movements, postural reflexes, support reactions. "The contraction of a muscle on being stretched may exist in latent form and become distinct, or apparent at all, only when there is a functional or an organic increase in muscle tonus." ". . . the appearance of some reflexes—usually latent—in the presence of a pyramidal lesion does not mean that the reflexes are new, but rather that they represent the pathologic exaggeration of normal reflexes which exist in latent form." This applies to such pyramidal reflexes as the Rossolimo, Troemner, Mendel-Bechterew, etc.

Many reflexes described in the literature, when considered on the basis of physiological interpretation, are identical with one another, such as the Rossolimo reflex, the Zhukovski-Kornilow, the Yoshimara reflex. They are one and the same reflex insofar as the same muscles are stimulated, even though by different methods. The

fact that one and the same reflex can be elicited from different points, was used by many investigators to claim that they had found a new reflex, which has led to great confusion in neurological nomenclature. "Since concussion of the muscle and its stretching constitute the true cause of the deep muscle reflex, the point from which this response may be achieved is not essential. It is irrelevant whether the concussion comes from the tendon, from the neighboring joints or from bone, or is obtained through a broad mass percussion of the muscle itself." "If, in interpreting and naming the reflexes, one shifts the focus of attention from the point of elicitation to the muscle whose action is provoked, an essential simplification, a better physiologic understanding and a distinct didactic advantage result."

Wartenberg does away with the distinction of tendon, bone, periosteal, osteo-periosteal, osteo-tendon, joint, fascial and aponeurotic reflexes, on the physiological basis that "the receptors of the 'tendon and periosteal' reflexes lie not in the tendon or in the periosteum but in the muscle itself." "From a neurophysiologic standpoint the tendon is, so to speak, passive, dead tissue, and no stimulation of the tendon can evoke any reflex action unless the muscle tissue is influenced through the tendon." Likewise, "the periosteum is only the point of application of the stretch stimulus." The same is true for joints, bones, etc. "These structures serve only to transmit the stretch stimulus. The deep reflexes are physiologically muscle stretch reflexes."

From the muscle stretch, or deep, reflexes, Wartenberg distinguishes the superficial, or "skin" reflexes. The stimulus is applied to the skin, without directly involving the mass of the muscle. It is a skin-muscle reflex, not a direct, but an indirect muscle reflex.

The bulk of the book consists in a detailed description of the various reflexes described in the literature, showing that many of them have different names only because described by several investigators, or because each method of elicitation of the reflex has been called a new reflex. The methods of elicitation and of reinforcement of reflexes are described, and their physiological as well as their clinical significance are discussed.

It should be obvious that clarification and simplification are indeed achieved by this approach, and the bewildering multiplicity of reflexes is reduced to a few reflex entities. One may doubt whether the author with this presentation achieves the goal of offering the student a really simple review of the reflexes in their relation to neurological diagnosis. For a review to be simple and readily understood by the medical student, the author perhaps deals too extensively with the conflicting claims of the various authors. Possibly the task of sifting the superabundant material made this unavoidable.

As an attempt to simplify and clarify neurological diagnostic procedures, and to explain their physiological and clinical significance, the book is of great practical and theoretical value. It contains a comprehensive bibliography (465 numbers), a subject and an author index.

H. W. L.

BOOKS RECEIVED

Books received during October are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Harvey Cushing. A Biography. By JOHN F. FULTON. 754 pages; 24.5 × 16 cm. 1946. Charles C. Thomas, Springfield. Price, \$5.00.

The Diagnosis and Treatment of Bronchial Asthma. By LESLIE N. GAY, M.D. Foreword by Warfield T. Longcope, M.D. 334 pages; 24 × 16 cm. 1946. Williams and Wilkins Company, Baltimore. Price, \$5.00.

- Leprosy*. Third Edition. By Sir LEONARD ROGERS, M.D., F.R.C.P., and ERNEST MUIR, M.D., F.R.C.S. 280 pages; 22 × 14.5 cm. 1946. Williams and Wilkins Company, Baltimore. Price, \$7.00.
- Treponematoses*. By ELLIS H. HUDSON, M.D. Edited by HENRY A. CHRISTIAN, F.A.C.P., F.R.C.P. 122 pages; 24 × 16 cm. 1946. Oxford University Press, New York. Price, \$2.50.
- Manual of Applied Nutrition*. Second Edition. Compiled by HELEN BAUGHMAN, KATHLEEN M. LEWIS and ELOISE R. TRESCHER. 103 pages; 19 × 13 cm. 1946. The Johns Hopkins Hospital, Baltimore. Price, \$1.50.
- Medical Uses of Soap*. A Symposium. By various authors. 195 pages; 23.5 × 15.5 cm. 1946. J. B. Lippincott Company, Philadelphia. Price, \$3.00.
- Las Neumopatías Aceitosas*. Estudio Clínico y Experimental. By various authors. Edited by EL ATENEO. 128 pages; 27.5 × 18.5 cm. Librería y Editorial "El Ateneo," Buenos Aires.
- Victory Over Pain*. A History of Anesthesia. By VICTOR ROBINSON, M.D. 338 pages; 22 × 15 cm. 1946. Henry Schuman, New York. Price, \$4.00.
- The Chest*. A Handbook of Roentgen Diagnosis. By LEO G. RIGLER, M.D. 352 pages; 21 × 14 cm. 1946. Year Book Publishers, Inc., Chicago. Price, \$6.50.
- Hygiene*. Fourth Edition. By FLORENCE L. MEREDITH, B.Sc., M.D. 837 pages; 24 × 16.5 cm. 1946. The Blakiston Company, Philadelphia. Price, \$4.00.
- Mongolism and Cretinism*. By CLEMENS E. BENDA, M.D. 310 pages; 24 × 15.5 cm. 1946. Grune and Stratton, New York. Price, \$6.50.
- Essentials of Medicine*. Fifteenth Edition. By CHARLES PHILLIPS EMERSON, JR., M.D., and JANE ELIZABETH TAYLOR, R.N., B.S., M.Ed. 688 pages; 21 × 14 cm. 1946. J. B. Lippincott Company, Philadelphia. Price, \$3.50.
- A Textbook of Clinical Neurology*. Second Edition, Revised. By J. M. NIELSEN, M.D., F.A.C.P. 699 pages; 26 × 18.5 cm. 1946. Paul B. Hoeber, Inc., New York. Price, \$7.50.

COLLEGE NEWS NOTES

LIFE MEMBERS

The College takes pleasure in announcing that the following Fellows have become Life Members of the College:

Dr. Henry M. Moses, Brooklyn, N. Y., October 23, 1946
Dr. Henry L. C. Weyler, Providence, R. I., November 4, 1946
Dr. W. E. G. Lancaster, Fargo, N. D., November 14, 1946

Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, has presented to the College Library of Publications by Members a copy of "Management of Common Cardiac Conditions," published by J. B. Lippincott Co. Edited by Dr. Leaman, the book contains selected presentations from the A.C.P. postgraduate course in Cardiology which was given in Philadelphia in the spring of 1946 under Dr. Leaman's direction.

AMERICAN BOARD OF INTERNAL MEDICINE EXAMINATIONS

The American Board of Internal Medicine has announced that oral examinations will be held at Chicago, February 12, 13, and 14, 1947 (closing date, January 1, 1947); at Chicago, April 24, 25, and 26, 1947 (closing date, February 15, 1947); and at Philadelphia, June 5, 6, and 7, 1947 (closing date, April 1, 1947). The written examination will be given by the Board on March 17, 1947, instead of February 17 as had been announced earlier.

Dr. Philip Levine, F.A.C.P., Raritan, N. J., Dr. Alexander S. Wiener, F.A.C.P., Brooklyn, N. Y., and the Army Epidemiological Board, of which Dr. Francis G. Blake, F.A.C.P., New Haven, Conn., has been chairman, received Lasker Awards at the recent meetings of the American Public Health Association. The awards are made for distinguished research on problems affecting the public health.

A.C.P. RESEARCH FELLOWSHIPS

The first of the College's Research Fellowships for the year 1947-48 has been awarded by the Committee on Fellowships and Awards, Dr. Reginald Fitz, F.A.C.P., chairman, and the Board of Regents to Dr. Tom Fite Paine, Jr., Aberdeen, Miss. The fellowship will enable Dr. Paine to continue studies of infectious diseases, with especial reference to chemotherapy and the use of antibiotics, in which he is presently engaged under the supervision of Dr. Maxwell Finland, F.A.C.P., at the Thorndike Memorial Laboratory of the Boston City Hospital.

Following completion of his medical course at Vanderbilt University in 1942, Dr. Paine interned at the Strong Memorial Hospital, Rochester, N. Y. During his subsequent service in the A.U.S., Dr. Paine received an assignment to Camp Detrick, and there participated in clinical and laboratory studies of infectious diseases.

A limited number of additional research fellowships will be awarded, to begin, in most cases, July 1, 1947, and to continue in effect for one year. Their purpose is to provide an opportunity for research training in the basic medical sciences or in the application of these sciences to clinical investigation for physicians who are in the early stages of their preparation for teaching and investigative careers in internal medicine and allied fields. The stipends vary from \$1800 to \$3000 for the year, according to the applicants' needs. Application forms may be had on request to The

American College of Physicians, 4200 Pine St., Philadelphia 4, Pa. Awards will be made on or about January 1, 1947; applications should be submitted as early as is possible.

A.C.P. REGIONAL MEETING, MEMPHIS

A Regional Meeting of the College for Arkansas, Louisiana, Mississippi, Tennessee and Texas was held at Memphis, November 22, through the coöperation of Governors Oliver C. Melson, Edgar Hull, John Archer, William C. Chaney and M. D. Levy. A feature of the meeting was the dinner in honor of Dr. Hugh J. Morgan, President-Elect of the College.

The scientific program was as follows:

1. Coronary Artery Disease,
William D. Stroud, M.D., F.A.C.P., Philadelphia.
2. Clinical Pathologic Conference,
Conley H. Sanford, M.D., F.A.C.P., William C. Colbert, M.D., F.A.C.P.,
and Douglas H. Sprunt, M.D., F.A.C.P., Memphis.
3. New Knowledge in the Treatment of Malaria,
H. Packer, M.D., Memphis.
4. Treatment of Intractable Peptic Ulcer,
Walter L. Palmer, M.D., F.A.C.P., Chicago.
5. Hypertension,
Hugh J. Morgan, M.D., F.A.C.P., Nashville.

Dr. Leonard G. Rowntree, F.A.C.P., Philadelphia, Pa., and Miami, Fla., has been presented with the Medal for Merit. The citation reads, in part: "as chief of the medical division of the Selective Service System from Dec. 18, 1940 to June 16, 1945 (he) anticipated, met and solved, with never failing diligence and professional proficiency, the ever changing medical problems which arose in the administration of the Selective Service System. . . . He merits the gratitude of the nation for his immense contributions to the mobilization of its manpower."

Dr. Lucian A. Smith, F.A.C.P., Rochester, Minn., is the recipient of the Bronze Star for his development of "a method for early diagnosis and effective therapy of various types of dysenteries." Dr. Smith's cited achievements were accomplished while he was on duty in the Medical Corps, A.U.S., in New Guinea in 1944-45.

In recognition of the forty years of distinguished service which Dr. Berthold S. Pollak, F.A.C.P., Jersey City, N. J., has rendered as Medical Director of the Hudson County Tuberculosis Hospital and Sanatorium, the county's Board of Chosen Freeholders took action on October 10, 1946, to change the name of the hospital to The Berthold S. Pollak Hospital for Chest Diseases.

AMERICAN TRUDEAU SOCIETY COURSE

A postgraduate course in Thoracic Diseases will be given at the University of Wisconsin Medical School, Madison, March 3-8, 1947, under the sponsorship of The American Trudeau Society. The registration is limited to thirty qualified physicians; priority will be given to residents of midwestern states. The fee is \$50. A prospectus of the course and application forms may be secured from Cameron St. C.

Guild, M.D., Executive Secretary, The American Trudeau Society, 1790 Broadway, New York 19, N. Y.

A course in Electrocardiographic Interpretation for *graduate physicians* will be given at the Michael Reese Hospital Postgraduate School by Dr. Louis N. Katz, Director of Cardiovascular Research. The class will meet each Wednesday from 7:00 to 9:00 p.m., for twelve weeks, beginning February 12.

Further information and a copy of the lecture schedule may be obtained upon application to the Office of the Dean, Michael Reese Hospital Postgraduate School.

RETIREMENTS FROM SERVICE

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to November 12, 1946 inclusive).

Francis J. Braceland, Chicago, Ill. (Capt., MC, USNR)
 Joseph E. Brackley, Boston, Mass. (Major, MC, AUS)
 Joseph L. Campbell, Ulster, Pa. (Lt. Col., MC, AUS)
 George D. Chunn, Sarasota, Fla. (Col., MC, USA)
 Joseph H. Delaney, Columbia, Mo. (Major, MC, AUS)
 Frank S. Dietrich, Portland, Ore. (Lt. Col., MC, AUS)
 Mackinnon Ellis, Bryn Mawr, Pa. (Comdr., MC, USNR)
 Waldo B. Farnum, New York, N. Y. (Col., MC, AUS)
 Ralph M. Fellows, Milwaukee, Wis. (Lt. Comdr., MC, USNR)
 Kenneth G. Gould, Tampa, Fla. (Col., MC, USA)
 Marshall W. Graham, Washington, Pa. (Lt. Comdr., MC, USNR)
 Milton E. Hubbard, Los Angeles, Calif. (Col., MC, AUS)
 Saul Jarcho, New York, N. Y. (Lt. Col., MC, AUS)
 Emory H. Main, Philippi, W. Va. (Capt., MC, AUS)
 Hugo Mella, Washington, D. C. (Col., MC, AUS)
 Frank L. Price, Youngstown, Ohio (Lt. Comdr., USPHS)
 Norman Reider, Los Angeles, Calif. (Major, MC, AUS)
 Lee Rice, San Antonio, Tex. (Col., MC, AUS)
 Paul Richmond, Jr., Worcester, Mass. (Capt., MC, USN)
 Joseph H. Shaffer, Detroit, Mich. (Lt. Col., MC, AUS)
 Ralph K. Shields, Bethlehem, Pa. (Major, MC, AUS)
 Oliver C. Wenger, Washington, D. C. (Sr. Surgeon, USPHS)
 Edward C. White, Alexandria, Va. (Rear Admiral, MC, USN)

AMERICAN COLLEGE OF PHYSICIANS POSTGRADUATE COURSES

No other activity of the American College of Physicians has met with greater enthusiastic support than that of its postgraduate courses. The demand greatly exceeds available facilities. These courses are looked upon as superior to any other work of the kind available in this country, and other groups have started to imitate our work. During 1946 the College organized twenty-three separate and distinct courses, ten during the Spring and thirteen during the autumn, with a registration in excess of 1200 physicians, chiefly Fellows and Associates of the College.

Many of the courses were oversubscribed.

The Spring, 1947 Schedule

The following list of courses are scheduled during the winter and spring of 1947. The Postgraduate Bulletin will be published on or about January 1, 1947, and will be

distributed to all Fellows and Associates of the College and to such other physicians as have requested that their names be placed on the mailing list. Reservations may be made in advance by communicating with E. R. Loveland, Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia, 4, Pa.

GROWTH, ISOTOPES, AND TUMOR FORMATION.

The Lankenau Hospital Research Institute and The Institute for Cancer Research, Philadelphia, Pa.

Stanley P. Reimann, M.D., F.A.C.P., Director.

February 3-8, 1947.

Fee: A.C.P. Members, \$40.00; Non-Members, \$80.00.

CARDIOVASCULAR DISEASE.

University of Southern California, Los Angeles, Calif.

George C. Griffith, M.D., F.A.C.P., Director.

February 3-7, 1947.

Fee: A.C.P. Members, \$20.00; Non-Members, \$40.00.

ARTHRITIS AND ALLIED CONDITIONS.

Mayo Foundation, University of Minnesota, Rochester, Minn.

Philip S. Hench, M.D., F.A.C.P., Director.

One week—March 24-29, 1947.

Fee: A.C.P. Members, \$20.00; Non-Members, \$40.00.

PERIPHERAL VASCULAR DISEASE.

Mayo Foundation, University of Minnesota, Rochester, Minn.

Edgar V. Allen, M.D., F.A.C.P., Director.

One week—March 17-22, 1947.

Fee: A.C.P. Members, \$20.00; Non-Members, \$40.00.

CARDIOVASCULAR DISEASE.

Emory University School of Medicine, Atlanta, Ga.

Bruce Logue, M.D., F.A.C.P., Director.

March 31-April 5, 1947.

Fee: A.C.P. Members, \$20.00; Non-Members, \$40.00.

INTERNAL MEDICINE.

University of Michigan Medical School, Ann Arbor, Mich.

Cyrus C. Strugis, M.D., F.A.C.P., Director.

April 7-19, 1947.

Fee: A.C.P. Members, \$40.00; Non-Members, \$80.00.

CARDIOVASCULAR DISEASE.

Northwestern University Medical School, Chicago, Ill.

J. Roscoe Miller, M.D., F.A.C.P., Director.

April 21-26, 1947.

Fee: A.C.P. Members, \$20.00; Non-Members, \$40.00.

CARDIOVASCULAR DISEASE.

Philadelphia General Hospital.

Francis C. Wood, M.D., F.A.C.P., and Calvin F. Kay, M.D., Directors.

One week—May 12-17, 1947.

Fee: A.C.P. Members, \$20.00; Non-Members, \$40.00.

INTERNAL MEDICINE, WITH EMPHASIS UPON NUTRITION AND METABOLISM.

University of Cincinnati College of Medicine, Cincinnati, Ohio.

Marion A. Blankenhorn, M.D., F.A.C.P., Director.

May 26-June 7, 1947.

Fee: A.C.P. Members, \$40.00; Non-Members, \$80.00.

28TH ANNUAL SESSION, A.C.P.

Chicago, Ill. (Headquarters: Palmer House).

David P. Barr, M.D., F.A.C.P., President.

LeRoy H. Sloan, M.D., F.A.C.P., General Chairman.

April 28-May 2, 1947.

Fee: A.C.P. Members, free; Non-Members, \$15.00.

Detailed Outline

COURSE NO. 1—GROWTH, ISOTOPES, AND TUMOR FORMATION

(February 3-8, 1947)

The Lankenau Hospital Research Institute and The Institute for Cancer Research
Philadelphia, Pa.

STANLEY P. REIMANN, M.D., F.A.C.P., *Director*

(Minimal Registration, 15; Maximal Registration, 30)

Fees: A.C.P. Members, \$40.00

Non-Members, \$80.00

Officers of Instruction

Oscar V. Batson, M.D., Professor of Anatomy, University of Pennsylvania Graduate School of Medicine.

Philip D. Bonnet, M.D., Director, The Lankenau Hospital.

Edward L. Bortz, M.D., F.A.C.P., Chief of Medical Service B, The Lankenau Hospital.

Robert Briggs, Ph.D., Department of Experimental Embryology, The Lankenau Hospital Research Institute.

Charles L. Brown, M.D., F.A.C.P., Dean, Hahnemann Medical College and Hospital of Philadelphia.

Clark E. Brown, M.D., Pathologist, The Lankenau Hospital.

Hugh J. Creech, Ph.D., Immuno-Chemist, Department of Immunity, The Lankenau Hospital Research Institute.

Lawrence Curtis, M.D., Associate Professor of Oral Surgery, University of Pennsylvania Graduate School of Medicine.

Earl A. Daugherty, M.D., F.A.C.P., Assistant Physician, The Lankenau Hospital.

J. Montgomery Deaver, M.D., F.A.C.S., Chief of Surgical Service A, The Lankenau Hospital.

- Irene C. Diller, Ph.D., Cytologist, Department of Cytology, The Lankenau Hospital Research Institute.
- Gilson Colby Engel, M.D., F.A.C.S., Chief of Surgical Service B, The Lankenau Hospital.
- Elizabeth U. Green, Ph.D., Experimental Embryologist, The Lankenau Hospital Research Institute.
- Mary A. Hamilton, Ph.D., Immuno-Chemist, The Lankenau Hospital Research Institute.
- Fred L. Hartmann, M.D., Chief of Medical Service A, The Lankenau Hospital.
- Theodore S. Hauschka, Ph.D., Micro-Biologist, The Lankenau Hospital Research Institute.
- John Kidd, M.D., Professor of Pathology, Cornell University Medical College, New York, N. Y.
- Theodore F. Lavine, Ph.D., Organic Chemist, The Lankenau Hospital Research Institute.
- William G. Leaman, Jr., M.D., F.A.C.P., Professor of Medicine, Woman's Medical College of Pennsylvania.
- Warren H. Lewis, M.D., Wistar Institute of Anatomy, Philadelphia, Pa.
- L. G. Livingston, Ph.D., Assistant Professor of Botany, Swarthmore College; Plant Physiologist, The Lankenau Hospital Research Institute.
- Hans May, M.D., Assistant, Surgical Service B, The Lankenau Hospital; Assistant Professor of Surgical Pathology, University of Pennsylvania Graduate School of Medicine.
- Jane R. McConnell, Ph.D., General Physiologist, The Lankenau Hospital Research Institute.
- Grace Medes, Ph.D., Physiological Chemist, In Charge of Isotope Research, The Lankenau Hospital Research Institute.
- Valy Menkin, M.D., Professor of Experimental Pathology, Temple University School of Medicine.
- Malcolm W. Miller, M.D., F.A.C.P., Assistant Physician, The Lankenau Hospital.
- Francis Ashley Montagu, M.D., Fellow of The Royal Anthropological Society of Italy; Staff Member, The American Museum of Natural History.
- Jesse T. Nicholson, M.D., F.A.C.S., Professor of Orthopedic Surgery, University of Pennsylvania Graduate School of Medicine.
- Jane Oppenheimer, Ph.D., Assistant Professor of Biology, Bryn Mawr College.
- Henry F. Page, Jr., M.D., F.A.C.P., Assistant Physician, The Lankenau Hospital.
- Daniel B. Pierson, Jr., M.D., F.A.C.P., Assistant Physician, The Lankenau Hospital.
- Allen Reid, Ph.D., Physical Chemist in Charge of Construction C-13 Plant, Sun Oil Company, Marcus Hook, Pa.
- Hobart A. Reimann, M.D., F.A.C.P., Professor of Medicine, Jefferson Medical College of Philadelphia.
- Stanley P. Reimann, M.D., F.A.C.P., Director, The Lankenau Hospital Research Institute and the Institute of Cancer Research; Associate Professor of Surgical Pathology, University of Pennsylvania Graduate School of Medicine; Professor of Oncology, Hahnemann Medical College and Hospital of Philadelphia; Chairman, Cancer Commission, Pennsylvania State Medical Society.
- Jack Schultz, Ph.D., Department of Genetics, The Lankenau Hospital Research Institute.
- R. R. Spencer, M.D., National Cancer Institute, Bethesda, Md.
- Gerrit Toennies, Ph.D., Organic Chemist, The Lankenau Hospital Research Institute.
- Charles A. W. Uhle, M.D., Urologist, The Lankenau Hospital.

Sidney Weinhouse, Ph.D., Organic Chemist, Houdry Process Corporation, Marcus Hook, Pa.

Philip R. White, Ph.D., Department of General Physiology, The Lankenau Hospital Research Institute.

General Statement

An advanced course designed to present the basic problems of growth and their application to various practical problems in medicine, such as physique, constitution, wound healing, regeneration, inflammation, congenital anomalies, and tumor formation. In this course medicine will be regarded as a branch of biology.

Beginning this subject, the basic factors will be presented by biologists and others in the fundamental field. The practical applications will then be considered and emphasized together with the problems presented in clinical practice.

The introduction of isotopes as tracers in studies of intermediary metabolism has been revolutionary. As in many other fields, isotopes as tracers have contributed knowledge to the growth problem. A whole day session will be devoted to isotopes—how they are used as tracers, what teams must be organized for their proper use, and the instruments for their measurement.

In the morning physicists will present the highlights of newer knowledge of the atom; biochemists will present results in special fields thus far opened. In the afternoon, a special trip has been arranged to the Houdry Process Corporation and the Sun Oil Company plants in Marcus Hook, a few miles south of Philadelphia. At these plants the apparatus for the preparation of stable isotopes, and the instruments for measuring them, as well as radioactive isotopes, will be inspected and demonstrated.

A morning session will be devoted to the biological problems of cancer. They will be discussed in a session devoted to this subject with a final paper on "Survival Time" by R. R. Spencer, M.D., of the National Cancer Institute. Finally, specific tumors will be presented and methods of diagnosis, treatment, and general management will be stressed.

Morning Meetings: The Lankenau Hospital Nurses Training School Auditorium
22nd St. & Girard Ave.

Afternoon Meetings: The Laboratory of The Lankenau Hospital Research Institute

Outline of Course

Monday, February 3.

Presiding: Dr. Bortz.

Growth is cyclical and is compounded of numerous separable processes each with its own set of starting, stimulating, regulating, inhibiting factors.

Differential growth—the various types of human beings determined by both heredity and environment. Classification of types, their strengths and weaknesses.

The establishment of growth patterns in early life as a basis for normal development.

The human constitution and its various patterns as related to particular disease states will be discussed.

A.M. Session.

9:00 Greetings and Introductory Remarks.

Officials of Hospital, Institute and The American College of Physicians.

- 9:30 Cycles of Growth.
Dr. Stanley P. Reimann.
- 10:00 The Varieties of Man and the Problems of Growth.
Dr. Montagu.
- 10:30 Normal and Pathologic Growth Patterns.
Dr. Batson.
- 11:15 Constitution and Disease.
Dr. Hobart A. Reimann.
- 12:30 LUNCHEON with members of Research and Hospital Staff.
- P.M. Session
- 2:00 Demonstrations and Conferences: (See descriptions) 1, 2, 3, 4, 5, 6, 7, 8, 9, 10.
- 5:30 Cocktails—Library of The Research Institute.

Demonstrations and Conferences

Three afternoons will be devoted to demonstrations and conferences. The students will be divided into small units, and each group will be assigned to a particular demonstration. The following problems will be taken up:

1. Special nutritional requirements for growth.
Dr. Bonnet. Significance of sulfur linkages, the methyl group. Intestinal and liver factors involved.
2. Cancer and protozoa.
Dr. Hauschka and Group. Experiments with trypanosomes and their products in mouse tumors. Specific tissue inhibitors such as hexenolactone.
3. The use of tissue cultures as a means of solving problem of growth.
Dr. McConnell and Group. Attempts to devise chemically known culture media. The effects of bacterial polysaccharide, emetin, hexenolactone and other substances on cell viability.
4. Proteins in cancer.
Drs. Toennies, Lavine and Group. Possibilities of differentiation from proteins in normal tissue. Properties of the amino acids and methods for their chemical and bio-assay. Newer findings in amino acid linkages and transmutations.
5. Immunity to carcinogens and to cancer itself.
Drs. Creech and Hamilton. The production of antisera and anti-antisera to the bacterial polysaccharide used in treatment of human sarcoma. Why antisera are necessary.
6. Cultures of both normal and cancerous plant tissues.
Dr. White and Group. A discussion of the usefulness in helping to solve problems in animal growth. What is learned from cancerous plant tissues in relation to abnormal human growths.
7. The control of differentiation as a prerequisite to a fundamental knowledge of the physiology of the cancer cell.
Drs. Briggs, Green and Group. Tumors in tadpoles. Nuclear transplantations. Production of rhabdomyosarcomas in mice. Possible viral etiology.
8. Methods for studying human chromosomes.
Dr. Schultz and Group. Chromosomes and genes. Their study by cytological, genetic, and chemical methods. The beginnings of a map of human chromosomes. The apparatus and technic of microchemical studies of enzyme activity.

9. Isotopes in metabolic studies.

Dr. Medes and Group. Methods of testing in whole animals, organs, tissue slices, tissue brei. What to look forward to when Isotopes become available in quantity for human study. How to organize a "Team" for this work.

10. The effect of *B. prodigiosis* polysaccharide and other agents on tumorous growths.

Dr. Diller and Group. The effect on mouse and human tumors. The hemorrhage and necrosis. The synergistic effect of x-rays and polysaccharide. The use of adrenal cortical extract with and without polysaccharide. The cytological details of cells in mitosis being destroyed.

Tuesday, February 4.

Presiding: Dr. Pierson.

Wound healing is compounded of proliferation, differentiation and organization of cells into tissues. Cell movements singly and en masse are necessary. The factors, local and general, stimulating and inhibiting these processes.

Inflammation and repair—Newer findings in capillary participation, fluid exchange, lymphatic drainage and their effect on repair.

Convalescence and regeneration—Factors which accelerate or impede convalescence and regeneration.

Transplantation of tissues, of organs, homoplastic, heteroplastic. Factors influencing. Transplantation of tumors. Their significance and value as test objects.

Reconstructive surgery—Principles; Illustrated by examples from various parts of the body.

A.M. Session.

9:30 Wound Healing and Its Cellular Physiology.

Dr. Lewis.

10:00 Inflammation and Repair.

Dr. Menkin.

10:30 Convalescence and Regeneration.

Dr. Charles L. Brown.

11:00 The Biological Background of Transplantation.

Dr. Briggs.

11:30 Applications of Wound Healing and Transplantation to Reconstructive Surgery.

Dr. May.

LUNCHEON

P.M. Session

2:00 Demonstrations.

3:00-5:00 Discussion of Demonstrations.

Wednesday, February 5.

Presiding: Dr. Miller.

Until recently growth anomalies were described anatomically. In modern investigations physiological and chemical explanations have been added. For example, Spemann's organizer phenomena. Chemical substances as too much calcium may cause anomalies. Infections such as German measles may lead to anomalies. Transplantation experiments have clarified genic and environmental factors to a considerable degree. The three germ layers are no longer valid. Human beings have regulatory

eggs as demonstrated among others by the Dionne quintuplets which are from one ovum, etc.

Head and neck—Hare lip, cleft palate, strabismus, ectopic salivary glands, thyroid, branchiogenic cysts and solid tumors, thyrohyoid ducts, etc., etc.

Cardiac anomalies—Some are compatible with long life, others with shortened life, some die at birth or before. The hereditary background. Certain operative procedures can be done as e.g., patent ductus arteriosus.

Urogenital—Horse shoe kidneys, double ureters, extrophia of bladder, undescended testes, etc. Diagnosis and treatment.

Extremities—Club feet, dislocation hip, short arm, etc.

A.M. Session

- 9:30 Physiological Causes of Growth Anomalies.
 Dr. Oppenheimer.
- 10:30 Growth Anomalies of the Head and Neck; Their Diagnosis and Treatment.
 Dr. Curtis.
- 11:00 Cardiac Anomalies and Life Expectancy.
 Dr. Leaman.
- 11:30 Growth Anomalies of the Urogenital System; Their Diagnosis and Treatment.
 Dr. Uhle.
- 12:00 M. Growth Anomalies of the Extremities and Their Correction.
 Dr. Nicholson.
- LUNCHEON

P.M. Session

- 2:00 Demonstrations.
- 3:30-5:00 Discussion of Demonstration Material.

Thursday, February 6.

Presiding: Dr. Daugherty.

Theory of isotopes—Present day conception of the structure of the atom. The transmutability of elements. Radioactive and stable isotopes. Choice for various problems.

Methods of separation and analysis—The thermaldiffusion and chemical methods of separation of stable isotopes. Methods of making radioactive isotopes. The mass spectrograph and the Geiger-Muller Counter.

Biological production—Methods of making by biological means the necessary compounds containing isotopes for human and animal work.

Fat metabolism—The use of heavy carbon for the study of fat metabolism. How fats are metabolized.

A.M. Session.

- 9:30 Theory of Isotopes.
 Dr. Weinhouse.
- 10:00 The Preparation and Analysis of Isotopes.
 Dr. Reid.
- 11:00 The Biological Production of Compounds.
 Dr. Livingston.
- 12:00 M. Studies in Fat Metabolism with Isotope Tracer.
 Dr. Medes.
- LUNCHEON

Afternoon: Visit to Houdry Process Corporation's Laboratory and Sun Oil Company Plant, Marcus Hook, Pa., to inspect apparatus for separating heavy carbon and instruments for measuring quantitatively both stable and radioactive isotopes. They are:

Thermal Diffusion Plants
Chemical Separation Plants
Mass Spectrograph
Geiger-Muller Counters.

Friday, February 7.

Presiding: Dr. Page.

Differentiation—The most important process leading to the different kinds of cells, tissues and organs; species specificity. Deviation of differentiation leads to tumors, benign and malignant, as well as to all other kinds of growth aberrations.

Chemical factors—The carcinogens. Immunity to conjugated products.

Genetic factors—The relation of cellular and organism inheritance to the predisposition to cancer.

Viruses and virus-like agents—Relation to special tumors and their relationship to tumor formations.

A discussion of "Survival Time" of lower species and the significance to human observations.

A.M. Session.

9:30 THE BIOLOGY OF TUMOR FORMATION.

The Problem of Cellular and Tissue Differentiation.

Dr. White.

Chemical Factors.

Dr. Creech.

Genetic Factors.

Dr. Schultz.

Viruses and Virus-like Agents.

Dr. Kidd.

STUDIES OF SURVIVAL.

Dr. Spencer.

REGIONAL MEETING, AMERICAN COLLEGE OF PHYSICIANS

P.M.

1:00 Luncheon Buffet—Headquarters of the College, 4200 Pine St., Philadelphia, Pa.

2:30 Scientific Program.

Ballroom, Warwick Hotel, 17th & Sansom Sts.

6:00 Reception.

Mezzanine, Warwick Hotel.

6:45 Dinner.

Mirror Room, Warwick Hotel.

After Dinner Program.

Edward L. Bortz, M.D., F.A.C.P., Toastmaster.

Introduction of Distinguished Guests.

Music by the Orpheus Club Male Octette.

Saturday, February 8.

Presiding: Dr. Bonnet.

A.M. Session.

9:30 Cancer of the Stomach.
Dr. Engel.

10:00 Cancer of the Colon.
Dr. Deaver.

10:30 The Leukemias.
Dr. Hartmann.

11:00 Peculiarities of Fibrosarcoma.
Dr. Clark E. Brown.

11:30 General Summary.
Dr. Reimann.

*OBITUARIES***DR. JAMES DEACON BRUCE**

James Deacon Bruce died at Ann Arbor, Michigan, on September 5, 1946, of cerebral hemorrhage. He was born at Blackstock, Ontario, on October 4, 1872, of Scotch-Irish ancestry, and named for his mother's favorite brother, Colonel James Deacon, born in Dublin, then with the Imperial Army in India. As a descendant of Adelme de Brus, the Normans of William the Conqueror, and the Scotch Highlanders of the Eleventh Century, he embodied the qualities of his Celtic-Anglo-Norman heritage. Conservative in action, strong in convictions, and intrepid in planning, his career followed the true course of his ancestry.

**JAMES DEACON BRUCE**

At the Detroit College of Medicine, which he entered in 1893, he earned his way by playing professional soccer and working in the office of Dr. Preston Hickey. On May 26, 1904, he was married to Grace Campbell, a loyal and intrepid Scotswoman, who survives him. Beginning practice in a small village, Dr. Bruce encountered the usual difficult situations common to the practice of medicine in those days. Ever resourceful, he made use of the measures at hand to care for the sick or protect the well. On one occasion, in 1898, he protected the inhabitants during an epidemic of smallpox by stretching barbed wire across all roads leading into the township.

In 1904 he came to the University of Michigan Medical School for post-graduate study and spent two years in the medical department under Dr. George Dock, Dr. David Cowie, and Dr. Hugo A. Freund. Following this period of study, Dr. and Mrs. Bruce located in Saginaw where they lived until 1925. Here Dr. Bruce practiced both medicine and surgery and attained distinction as a surgeon.

During World War I, Dr. Bruce joined the Canadian Army in early 1916, served as captain in the medical corps, and was chief of the medical service at the Duchess of Connaught Hospital near London. When we entered the war, he transferred to the United States Army Medical Corps, joining the Grand Rapids Unit at Camp MacPherson, Atlanta, Georgia, and went to France in March, 1918, to serve in evacuation hospital No. 5, at Auteuil, where his ability as an administrator and director quadrupled the capacity of the hospital.

One of his experiences during his military service is recalled. He was sent on an inspection trip to Ireland. While on ward rounds at the hospital in Dublin Castle, he was shown a soldier with an unhealed, painful shrapnel wound of the thigh, which had not been immobilized in a cast. In the presence of the resident staff, the chief surgeon of the hospital said ironically, "Major Bruce, as an American officer inspecting our methods of practice, no doubt you have an opinion about the care of this case." To this Dr. Bruce replied. "Colonel, you do not have to ask me for an opinion. Simply glance at the inscription above the door of this ward." The inscription was "Rest and Pain" by James Hilton.

Soon after he returned to private practice in Saginaw, he was chosen as councilor of the Michigan State Medical Society. He served in this capacity from 1923 to 1934. This experience seemed to have crystallized certain principles, and during his official association with the Society, his efforts were thenceforth directed towards the improvement of the *quality* of medical service. Recognizing also that the cost and distribution were factors affecting the standards of medical service, he exerted every effort to develop a common understanding in formulating plans to meet these problems by a constantly improving quality of medical service.

In 1925, Dr. Bruce discontinued private practice, including surgery, and removed to Ann Arbor where he became Director of the Department of Medicine at the University of Michigan Medical School.

Two years later, upon petition of the Council of the State Medical Society to the University Regents, he was made Director of a newly created Department of Postgraduate Medicine. He consistently refused a professorial rank because, I think, there was no available professorship of "People working together for an Ideal." Observations made in practice concerning the need for the continuing education of the physician and his conviction that the future course of the medical profession would be identified with the quality of its service were the motives that impelled him to develop an educational program for the benefit of medical graduates. It was hoped to make each community as self-sufficient as possible with respect to health and medical service by postgraduate study and the improvement of community hospital teaching facilities.

Convinced that a graduate need was being neglected by educational leaders and that the *obligation of any university faculty to its students does not end with the granting of a degree*, Dr. Bruce spared no effort to bridge the gap between the classroom, the laboratory, and the application of newer knowledge to daily life. During fifteen years of service in charge of medical postgraduate education at the University of Michigan, he created and supervised a program designed to reach physicians in every community. With the full coöperation of the local physicians, modern hospital buildings and adequate laboratory facilities were provided by the Couzens' Children's Fund at Marquette and Traverse City, manned by University staff members under his stimulus, and dedicated to improvement of medical care of children by the extension of educational opportunities to the physicians of the local areas. *No such development of medical care and postgraduate and graduate training had ever been seen before in America.*

Dr. Bruce was made a Fellow of the American College of Physicians in 1925, was elected its Governor for Michigan in 1930 and in 1936 was elected to its Board of Regents. In 1939 he was elected President-Elect and served as President, 1940-1941. He was again returned to the Board of Regents in 1941 and served until 1946. He exerted a real influence in the decision for the College to acquire its present home at 4200 Pine Street, Philadelphia. During a debate among Regents and Governors of the College at the Annual Session of the College in Detroit in 1936, when opinion upon the acquiring of a College home was divided, his summary of the needs and desirability of an adequate and dignified College Headquarters unified the opinions of all present and resulted in an unanimous vote in favor of the project, to the everlasting approval and satisfaction of all members thereafter.

One of the last acts of Dr. Bruce before his death was the outright gift of \$10,000.00 to the American College of Physicians, \$5,000.00 for the establishment of a periodic Service Award in memory of the late Dr. Alfred Stengel, who in the middle 20's was responsible for widespread reorganization and reforms in the College and who had a great influence on building the College as it is known today; and \$5,000.00 for the establishment of a Lectureship in preventive medicine. The Board of Regents thereupon estab-

lished "The James D. Bruce Fund" and designated the latter part of the bequest as "The James D. Bruce Lectureship in Preventive Medicine." Furthermore, Dr. Bruce designated the American College of Physicians as one of the chief legatees under his will.

Dr. Bruce, while deeply interested in every activity of the College, probably made his greatest contribution to the growth and increasing influence of the College through the development of an educational program. Indeed, the policy of the College with respect to its ultimate function in American medicine was greatly stimulated by Dr. Bruce in his address upon being inducted into the Presidency in 1940; when he said: "The College has assumed certain obligations which include the establishment of programs of education designed to keep our members at desirable levels of proficiency, the organization of resources to permit worthy candidates to prepare themselves to be accredited by the Board of Internal Medicine, and membership in the College, and the encouragement and support of research. The effective integration of all these functions justifies our use of the term 'college'." How much this "integration of resources" (wherever they may be found) has meant to us during the postwar period!

The ideals inspired by experiences in medical graduate education were soon to be applied by integration and expansion of the available resources of the University of Michigan in more general graduate and postgraduate education. In 1931 Dr. Bruce was appointed Vice-President in Charge of University Relations at the University of Michigan. In his request to Dr. Bruce to accept this position, President Ruthven said in behalf of the University Regents and himself, "We would like frankly to adopt the policy that the University should elaborate postgraduate study service, and institutional coöperation, and we want a man to direct these activities in a large way. The movement of adult education is really revolutionary and challenges the imagination."

The attraction of this position was chiefly that it gave opportunity to correlate various educational units of the state according to their functions and relations with the world outside the campus. The Division of Health Sciences and the Division of Extramural Services were organized. The extramural teaching activities were greatly increased, and a building in Detroit was constructed to be used jointly by the Detroit Engineering Society and the University for its extramural teaching program.

An important point is that *All* teachers in the state, regardless of college affiliations, were utilized in a plan for education toward better citizenship. Rivalry between schools yielded to reason when the United States was fast losing its democratic form of government. Following the principles of Jefferson, Monroe, and Madison, laid down at Red Gap, Virginia, he discerned that education for leadership in the *forms of Anglo-Saxon democracy* would be the only method of saving it, and that universities held chief responsibility. Dr. Bruce was able to bring all state organizations into a

common working agreement toward the objective of preserving a democratic government by means of adult education.

In general, Dr. Bruce examined the educational field in relation to a hereditarily determined background, in conformity with human nature, and without pedagogical prospectus. He presented to the educational system of our country the viewpoint that medieval intramural scholasticism was not conducive either to intellectual or political freedom and that the concepts of Anglo-Saxon democracy depended upon a continuing of extramural opportunity.

After his retirement from the University at the age of seventy years, Dr. Bruce devoted much of his time to the direction of a statewide program of adult education. He served as President of the Michigan Council on Adult Education from 1941 to 1944.

As an expression of his interests, and of the demands upon his time, a few of his organizational interests are mentioned:

Vice-President in Charge of University Relations, 1931-42; Member of Executive Committee of the University Medical School, 1930-42; Medical Adviser to the University Health Service, 1925-42; Chairman, Division of Health Sciences, 1935-42; Chairman, Division of Extramural Services, 1936-42; Medical Advisory Committee of National Committee on Economic Security, Member, 1934; National Research Council, Division of Medical Sciences, Committee on Medicine, Member, 1940-42; National Commission on Graduate Medical Education, Member, 1937-40; Associated States Postgraduate Committee, Chairman, 1937-40 and 1941-; Michigan Tuberculosis Sanatorium Commission, Member, 1932-; Michigan Council on Adult Education, President, 1941-; Michigan Committee on Juvenile Delinquency, Member, 1943-; Michigan Adult Education Advisory Committee, Member, 1944-.

In his personal relationships, Dr. Bruce was gracious, kindly, and companionable. His chief diversions were the English classics, especially Goldsmith, golf, and a consuming interest in horses. He was an inspiration to those who worked with him, and while skilled in knowledge of the frailties of human nature and unexcelled as a true physician, he was a fearless defender of the principles and ideals of western civilization. Intellectually honest and courageous he never compromised a fundamental principle, and injustice was especially not tolerated. *One characteristic we can all emulate was his ability to persuade men to work together toward an ideal.*

H. H. RIECKER, M.D., F.A.C.P.

DR. GEORGE THOMAS TWYMAN

George Thomas Twyman, Independence, Mo.; born at Independence, Mo., March 22, 1888; A.B., 1913, University of Kansas; M.D., 1915, Rush Medical College, Chicago; for many years attending physician, Independence

Sanitarium and Hospital; member of courtesy staff, Research, St. Joseph and Menorah Hospitals; member, Jackson County Medical Society, Missouri State Medical Society, American Medical Association and a Fellow of the American College of Physicians since 1931; died, October 4, 1946, at the Independence Sanitarium and Hospital of diabetes mellitus and cardiac failure.

Dr. Twyman was known for his qualities of leadership and fairness and set an example in his community for his fellow-physicians to imitate. Familiarly known as Dr. Tom, he was tall, handsome with a magnetic personality. Like his father, he was the leading physician in Independence and his passing was a personal loss to many.

RALPH KINSELLA, M.D., F.A.C.P.,
Governor for Missouri

DR. ARA NATHANIEL SARGENT

Ara Nathaniel Sargent, Salem, Massachusetts, born December 30, 1867; M.D. 1893, Harvard University Medical School; served many years on the staff of the Salem Hospital; Associate of the American College of Physicians since 1920 by virtue of membership in the American Congress of Internal Medicine; died at the Salem Hospital, August 26, 1946, at the age of seventy-eight.

Dr. Sargent was considered a very valuable consultant in internal medicine in his community, and was the father of the Salem Hospital laboratory. For many years he took entire charge of it and continued his interest in an active way up to the time a resident pathologist was appointed. He was the first physician in Salem to own a blood pressure apparatus and a blood counting chamber, both of which he brought from Europe about 1904.

His judgment and sound advice were much sought after by the physicians in Salem. He always took a great interest in the training school for nurses, and for a long time taught them their laboratory work and their courses in medicine. This interest in the nursing profession he activated in his will, inasmuch as he left a certain sum of money for a scholarship fund for nurses, another fund for books for the nurses' library, and a sum for the nurses' alumnae fund. He did not forget their enjoyment, and left a small fund to maintain their parties at Christmas time.

Dr. Sargent never married, and never went about in society, but he was very fond of travel. He made many trips to Europe, to the West coast, to the Caribbean Sea and to the West Indies. His hobby was collecting fine watches and instruments of precision, such as barometers. He had a large fund of general knowledge, and was particularly versed in the knowledge of precious stones and was often consulted as to their value.

He was a man who was highly respected and admired in his community, and his contributions to the Salem Hospital were very outstanding. He

will be remembered by all his colleagues and friends as one of the outstanding physicians in his community during his life.

CHESTER S. KEEFER, M.D., F.A.C.P.,
Governor for Massachusetts

DR. ANDERS FRICK

Dr. Anders Frick, F.A.C.P., Chicago, Illinois, was born in Malmoe, Sweden, January 12, 1868. He attended Malmoe Gymnasium and the University of Lund and received his Degree of Doctor of Medicine from the Karolinan Medical and Surgical Institute (Stockholm, Sweden) in 1896. Soon after receiving his degree, he migrated to this country and began practicing on the North Side of Chicago.

He was Attending Physician at Augustana Hospital, 1903 to 1925, Cook County Hospital, 1912 to 1913, and Assistant Professor of Medicine, University of Illinois Medical School, 1922 to 1929. He was a member of the Illinois Medical Society, Chicago Medical Society, Chicago Society of Internal Medicine, Institute of Medicine, American Medical Association and a Fellow of the American College of Physicians since 1920.

In 1925, Dr. Frick became Chief of Staff of Augustana Hospital and served in this capacity until his retirement in 1938. He died at the Augustana Hospital on May 9, 1946, at the age of 78.

Dr. Frick was an internist who represented the highest in the fine tradition of medical men of the older school. He was an upright gentleman, kind and understanding, and it was with great respect that patients and fellow physicians approached him. He was a capable teacher and trained many young men in the practice of general medicine.

With the passing of Dr. Frick, we have lost one who in every real way combined the finest qualities of both the old and new in the medical world.

ROBERT W. KEETON, M.D., F.A.C.P.

DR. ALEX MORTON ROSENBLUM

Dr. Alex Morton Rosenblum (Associate), Youngstown, Ohio, died September 6, 1946, of myocardial infarction.

Dr. Rosenblum was born on January 6, 1890. He graduated in Medicine from the University of Pennsylvania School of Medicine, Philadelphia, in 1912. For a number of years he was on the staff of the St. Elizabeth's Hospital. He served during World War I.

Dr. Rosenblum was a member of the Mahoning County Medical Society and the Ohio State Medical Association, and a Fellow of the American Medical Association. He became a member of the American Congress on Internal Medicine in 1920, and when that organization was merged with The American College of Physicians, Dr. Rosenblum automatically became an Associate of the latter.

DR. WAYNE WILLIAM BISSELL

Wayne William Bissell, Rockford, Illinois, was born in Lodi, Wisconsin, June 18, 1886. He took his pre-medical work at the University of Wisconsin from 1905 to 1909, and graduated from Rush Medical College in 1911. He served as intern at the Cook County Hospital, and later as a pathologist, 1913-1916. In July, 1916, he was appointed to the staff of the Mayo Clinic and remained there until World War I, when he accompanied the Mayo Unit in France. Since then he has served as pathologist and roentgenologist in Columbia, South Carolina; Reading, Pennsylvania, and New Castle, Pennsylvania. In September of 1945, he came to Rockford, where he served as pathologist at the Rockford Memorial Hospital.

Dr. Bissell was the author of a number of published papers; member of county and state medical societies and A.M.A.; Fellow of the American College of Physicians since 1931. He died of a coronary attack on September 6, 1946. He had the respect of his medical associates, and will be greatly missed.

CECIL M. JACK, M.D., F.A.C.P.,
Governor for Southern Illinois

DR. LEWIS TILGHMAN STONEBURNER, III

Dr. Lewis Tilghman Stoneburner, III, of Richmond, Va., is presumed to have died in action with the Army of the United States on November 10, 1944. This represents all the information available from the War Department.

Dr. Stoneburner was born in Richmond, Va., March 2, 1913. He received his B.A. degree from the University of Richmond and his degree of Doctor of Medicine from the Medical College of Virginia, 1937.

He was an Assistant in Medicine at Harvard Medical School, 1939-40, and from 1940 to the time of his entry into the Army he was an Assistant in Medicine at the Medical College of Virginia, Richmond. Dr. Stoneburner was Assistant Physician to the Hospitals of the Medical College of Virginia and a member of the medical staff of the Sheltering Arms Hospital.

He was a member of the Richmond Academy of Medicine, the Virginia Medical Society, and a Fellow of the American Medical Association. He had been an Associate of The American College of Physicians since 1943. He was the son of Dr. Lewis Tilghman Stoneburner, Jr., of Richmond, Va.

He was a Captain in the Medical Corps of the Army of the United States. He is reported to have taken off from Algiers to Tunis aboard a B-25 bomber as a passenger. He had been detached from General Hospital No. 45 and was attached to Medical Headquarters under Colonel Perrin Hamilton Long. His duties were to visit the various hospitals and secure certain data for the high medical command. Nothing was ever heard from the plane after its departure.

DR. JULIUS ORD ARNSON

Dr. Julius Ord Arnson, aged 58, died Tuesday, October 29, 1946, after an illness of one week. He was born in Eau Claire, Wisconsin, on July 3, 1888, of Norwegian parentage. He graduated from high school there, attended Hamline University, the University of Minnesota and was graduated from Northwestern University Medical School in 1911.

Dr. Arnson interned at St. Barnabas Hospital in Minneapolis after which he practiced in Kimball, Minnesota, before entering upon his specialty.

Well known throughout the Missouri Slope area, he came to Bismarck in 1915 where he was associated with the Quain and Ramstad Clinic in internal medicine and which department he headed. He was a leading heart specialist of the Northwest and saved the lives of an untold number of people with the same disease of which he himself succumbed.

He did postgraduate work in Boston, Massachusetts, and during World War I he was on the medical staff of Base Hospital 64, serving in France. He was a member of the American Legion, Sixth District Medical Society, North Dakota State Medical Association, American Medical Association, and a Fellow of the American College of Physicians of which he was Governor for many years. He was an associate editor of the *Journal-Lancet*, a member of the Blue Lodge and a 32nd degree Scottish Rite Mason.

For many years he was physician to the North Dakota State Penitentiary, which added to his labors as a busy internist. He only did this as a contribution to man. He made many visits to large penal institutions of this country in order to gain information as to the best method of treating these unfortunates, and applied the principles which he had learned with the limited facilities he had to work with.

Dr. Arnson was not only a competent physician but a humanitarian and a philanthropist. He despised sham and hypocrisy and was outspoken in his convictions. He was especially kind to the underprivileged.

Dr. Arnson never married, but maintained a home for his friends, as he was a most gracious and unselfish host. He had only one survivor, Dr. J. M. Arnson of Benson, Minnesota.

He had a marked natural literary ability, and he anticipated retiring on his ranch—which was his only hobby—where he had intended to write his memoirs of a prairie physician, for he had accumulated many letters and personal poems which he had planned to embody in this contribution.

Dr. Arnson was modest and never sought publicity for his good deeds, and had only a few confidants who knew of his personal affairs.

He had no particular religious affiliations, but his contributions to various church and civic organizations go unreported. His living deeds adorn his memory as he was a true brother of man.

C. W. SCHOREGGE, M.D., Bismarck, N. D.

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*The
Season's Greetings*



To lay a log of wood upon the fire
To dress the fir tree in its gift attire
To wish you happiness and cheer
To bring you peace throughout the year.



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FORT WARR, INDIANA

ANNALS OF INTERNAL MEDICINE

OFFICIAL PERIODICAL OF THE AMERICAN COLLEGE OF PHYSICIANS

Place of Publication—Prince and Lemon Sts., Lancaster, Pa.

Editorial Office—University Hospital,
Baltimore, Md.

Executive Office—4200 Pine Street,
Philadelphia, Pa.

THE ANNALS OF INTERNAL MEDICINE is published by the American College of Physicians. The contents consist of contributions in the field of internal medicine, editorials, book reviews, and a section devoted to the affairs of the College.

MANUSCRIPTS. All correspondence relating to the publication of papers and all books and monographs for review should be addressed to the editor. No manuscripts will be accepted without his consideration. Bibliographic references are to conform to the following style:

4. Doe, J. E.: What I know about it, Jr. Am. Med. Assoc., 1931, xcvi, 2006-2008.

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